12-2014

Effects of oxytocin on human aggression

Joseph L. Alcorn III

EFFECTS OF OXYTOCIN ON HUMAN AGGRESSION

by

Joseph Louis Alcorn III, B.S.

APPROVED:

_____

Scott D. Lane, Ph.D., Supervisory Professor

_____

Anne B. Sereno, Ph.D.

_____

Richard A. Meisch, M.D., Ph.D.

_____

Anthony A. Wright, Ph.D.

_____

Kevin A. Morano, Ph.D.

APPROVED:

_____

Dean, The University of Texas

Health Science Center at Houston

Graduate School of Biomedical Sciences

EFFECTS OF OXYTOCIN ON HUMAN AGGRESSION

A DISSERTATION

Presented to the Faculty of The University of Texas Health Science Center at Houston and The University of Texas M. D. Anderson Cancer Center Graduate School of Biomedical Sciences in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

Joseph Louis Alcorn III, B.S.

Houston, Texas

December 2014

joe.l.alcorn3@gmail.com

ACKNOWLEDGMENTS

My graduate career has been nothing but fantastic. I must first give thanks to my advisor, Dr. Scott Lane. Words cannot express how grateful I am for your patience and encouragement. You allowed me the independence to conduct my own research and for that I am grateful. In the face of all my successes and failures, your advisement has allowed me to grow from being a student to a scientist.

I am grateful for every person on my advisory committee. Dr. Anne Sereno, I thank you for being a stellar person who has been present throughout my graduate career. I thank you for taking the time to provide helpful feedback of my projects and for all the teaching opportunities that you gave me. Dr. Richard Meisch, your never-ending support and advice have helped me become a well-rounded scientist. I have tremendously enjoyed every single one of our conversations about science, life, and how to become a better person by self-management. Dr. Anthony Wright, I thank you for your solid advice, attention to detail, and love of science. Your dedication to helping students and ardor for learning has been an inspiration to me. Lastly, I give special thanks to Dr. Kevin Morano. It is no easy task to advise someone who is outside of your area of expertise, but your dedication to high caliber research and insightful advice has helped me grow substantially as a scientist.

I must thank all of the past and present members my wonderful laboratory, the Center for Neurobehavioral Research on Addiction, for the always being supportive of my research and interested in my project. These past five years with every single one of you have been a tremendous source of enjoyment and fun.

Thank you to all of my past and present classmates in the Neuroscience

Program. We have had some great times, shared more laughs than I can count, and we have always been supportive of one another. It is tempting to see your classmates as competitors. Instead, we saw each other as friends. I must also thank all the friends that I have made outside of the graduate school. Every single one of my friends have been a source of laughter and showed me that sometimes, you just need to leave the laboratory. I must also give thanks to all of the graduate school faculty and administrators who have always been a smiling face and helping hand. Joy Lademora, thank you for your love of student progression and life, and for all the free food that you gave me. Brenda Gaughan and Tracey Barnett, I thank you for always being helpful and at several times, lifesavers. Dr. Marenda Wilson-Pham, I will never forget all of the groundwork you did for the Association for Minorities in Biomedical Research. Dr. Shane Cunha, I thank you for being the forefront of career development and for all the career advice that you have given me over the years. Dr. Michael Blackburn, you served on two of committees and were present at the formulation of this project. I thank you for all of the input you gave me in the beginning and for being a spectacular dean.

Importantly, I have to thank my family; in particular, my dad, without whom I would literally not be here. You have been my biggest role model and you have always allowed me to be free to live my life the way I see it. To my sister Lola, we may fight but, I love you and I'm glad you're my sister.

Lastly, I must thank the very first participant that I ran in this dissertation. Simply because this person, unknowingly, gave me the quote that became my mantra for this project; "the science is on you."

EFFECTS OF OXYTOCIN ON HUMAN AGGRESSION

Joseph Louis Alcorn III, B.S.

Advisory Professor: Scott D. Lane, Ph.D.

Human interaction is comprised of common, yet complex, behaviors and the outcomes of these social behaviors can beneficially or detrimentally impact individual and public health. One social behavior that can have profound detrimental outcomes is aggression. Aggression is a class of social behavior that is particularly prevalent in individuals with antisocial personality disorder (ASPD) and comorbid substance use disorder (SUD). Aggression in these individuals can manifest at maladaptive levels that place considerable burdens on public health and communities. Therefore, understanding the neurobehavioral underpinnings of aggression holds substantial merit. The goal of this project was to examine the effects of this oxytocin (OT) on human aggression. Considerable work has demonstrated that OT engenders the promotion of affiliative social behaviors that are mutually beneficial (or prosocial) between two individuals. Aggression is characterized, in part, by social behaviors that are antisocial (which are opposite to prosocial behavior). The hypothesis was that acute administration of OT would reduce the frequency of human aggression. This hypothesis was tested in both individuals with comorbid ASPD and SUD, and healthy volunteers.

This project employed a well-established laboratory measure of human aggression, the Point Subtraction Aggression Paradigm, which measures changes in the frequency of aggressive behavior. In ASPD+SUD individuals there was no significant reduction in aggressive behavior following OT administration. However, there were non-systematic individual differences on aggressive behavior following OT dosing, which suggested modulation of aggressive behavior by OT. In healthy volunteers there was no significant effect of OT dose on aggressive behavior. However, in healthy volunteers, an examination of individual differences focused on antisocial personality traits revealed that aggressive behavior under OT was positively correlated with interpersonal manipulation and anger (Pearson's $r = 0.57$). Healthy volunteers with higher scores of interpersonal manipulation and anger actually showed an increase in their aggressive behavior following OT administration.

In both ASPD+SUD individual and healthy volunteers, the hypothesis that OT would decrease human aggression was not supported. The experiments of this dissertation revealed substantial individual differences in aggression following OT administration, which is important for future research in examining the therapeutic efficacy of OT for the management of aggression in antisocial and substance abuse populations.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1: INTRODUCTION

Human aggression

Human social interaction is comprised of complex dynamic behaviors. The consequences of human social interaction can be beneficial or detrimental to an individual's daily life and to the community as a whole. In the latter case, social interaction can be maladaptive and problematic. One enduring and problematic social behavior is aggression.

A seminal review paper of human aggression notes "In its most extreme forms, aggression is human tragedy unsurpassed" (Anderson & Bushman, 2002, pg 28). To many people, the word 'violence' is interchangeable with the word 'aggression'. However, aggression is specifically used to describe a wide range of behaviors; whereas violence is aggression that uses extreme or physical harm as its goal (e.g. assault and/or death) (Anderson & Bushman, 2002). Aggression is generally defined as any social behavior in which an individual presents an aversive stimulus to another individual, who finds the aversive stimulus harmful and would seek to avoid it (Baron & Richardson, 1994). Under this definition, two main classes of aggression emerge: impulsive aggression and premeditated aggression. Impulsive aggression is hostile, reactive, and anger-driven, whereas proactive aggression is instrumental, premeditated, and goal-driven (Bushman & Anderson, 2001). Impulsive aggression and premeditated aggression are hypothesized to both exist on a dimension rather than as two distinct categories, as aggressive acts typically contain elements of both impulsive and premeditated aggression (Bushman & Anderson, 2001). Conceptually, the experiments within this dissertation project

will focus on impulsive aspects of human aggressive behavior and the biopsychosocial relevance of impulsive aggression research to mental health with regard to modulation by oxytocin.

A widely accepted psychological theory used to describe human aggression is the General Aggression Model (GAM). The GAM is a theoretical and integrative model which posits the factors that occasion aggressive acts. The GAM focuses on processes occurring during one cycle or "episode" of an ongoing social interaction in which aggression may or may not occur. These processes can be thought of as foci. There are three foci: (i) person and situation inputs, (ii) the present internal state in which cognition, affect, and arousal all act as routes that mediate the impact of the person and the situation inputs, and (iii) outcomes that arise from the appraisal and decision processes that underlie aggressive action (i.e. deliberate or impulse action). The GAM provides an important theoretical framework that can be used to integrate many different hypotheses and theories of human aggression into one unified model. Though this model will not be directly tested in this dissertation, the theoretical framework of the GAM serves as an operational model for defining, testing, and understanding aggressive behavior. The conceptualization of the GAM gives credence to the examination of aggressive behavior during a social interaction for the experiments of this dissertation.

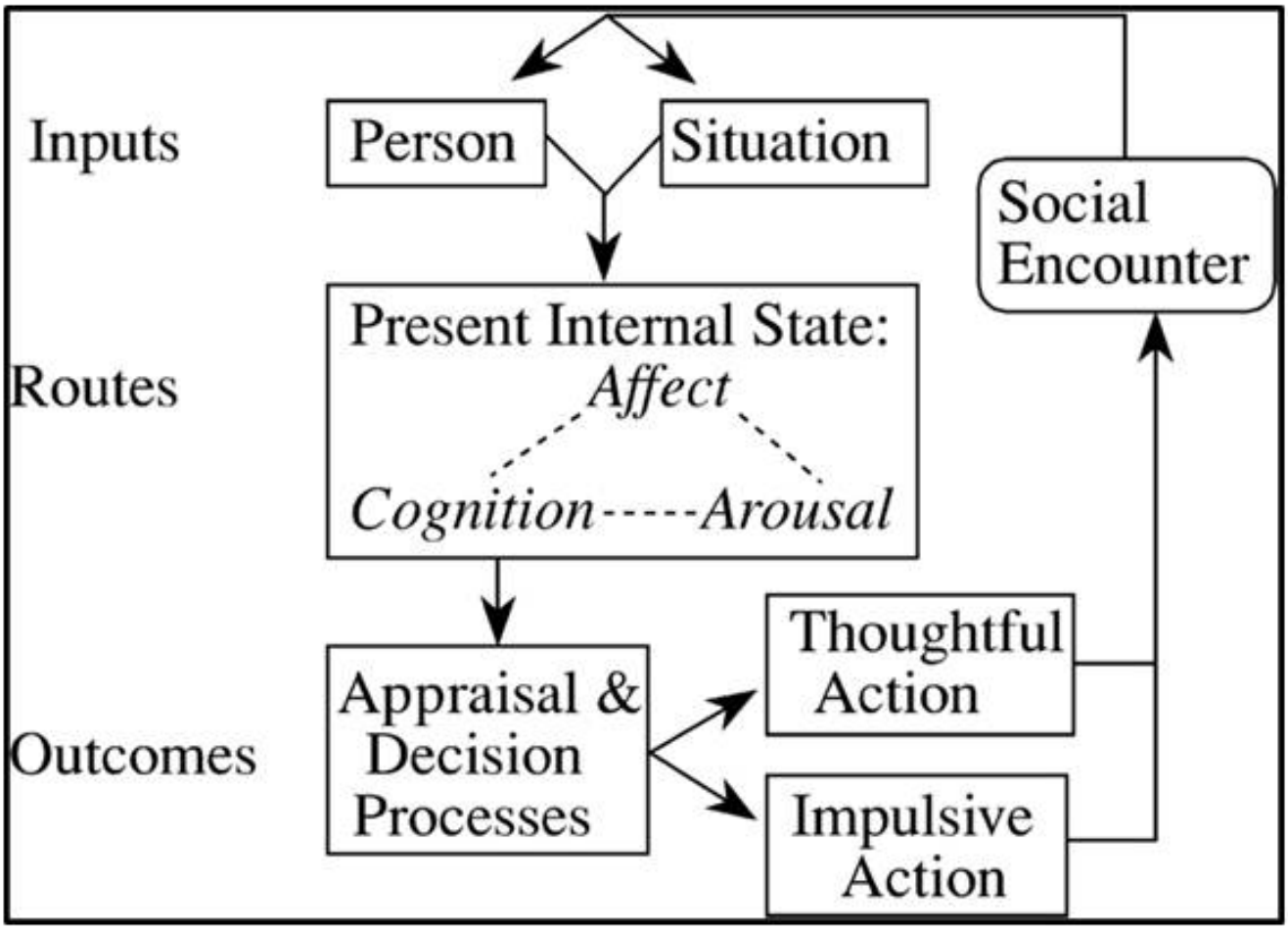


Figure I.A: The episodic processes that occur in the General Aggression Model (GAM) This model describes the three foci (inputs, routes, and outcomes) that governs the probability of an aggressive act. (Anderson, CA & Bushman, BJ (2002) Human Aggression. Annu Rev Psychol 53: 27-51; material may be used in a thesis without additional permission as stated by Annual Reviews).

The GAM provides a psychological framework for understanding an aggressive interaction (Figure I.A). During a social encounter in which aggressive acts could occur, there are inputs which influence the present state of the individual. These inputs exist as personal and situational factors. Personal factors are characteristics such as personality traits, beliefs, values, and gender. Situational factors include provocation, frustration, aversive stimulation, and aggressive cues. Personal and situational factors are inputs

that can increase the probability of aggressive acts by activating cognitive, affect, and arousal knowledge structures present within the individual. These knowledge structures then influence the decision to impulsively or thoughtfully act. The framework of the GAM provides identification of the psychological, environmental, biological, and social factors which influence aggression, including cases in which aggression is extreme or maladaptive.

Understanding complexity of aggression requires knowledge drawn from converging evidence in psychiatry, affective and cognitive neuroscience, psychopharmacology, and comparative psychology. However, the experiments within this dissertation are focused on examining human aggression within the context of neurobehavioral models of human social interaction. The experimental goals of this dissertation are to generate data that may be both experimentally and clinically significant. The overarching goal for this dissertation is two-fold: (i) to provide information about possible therapeutics for aggression and (ii) to further basic understanding of human aggression.

Clinical relevance: Antisocial Personality Disorder and Substance Use Disorder

The consequences of human aggression extract a substantial detrimental toll on criminal justice systems, mental health institutions, communities, families, and individuals. Approximately 1.6 million lives are lost each year as a result of human aggression, worldwide (Dahlberg, 2007). Further, acts of extreme aggression (i.e. violence) cost billions in U.S. dollars

each year, particularly costs in health care, legal systems, work productivity, and economic development (Anderson, 1999; Dahlberg, 2007). The harmful consequences of aggression are prominent in cluster B personality disorders. The cluster B personality that will be central to the experiments in this dissertation is Antisocial Personality Disorder (ASPD). Diagnosis of ASPD occurs in approximately 3-6% of the adult population (Anderson et al., 1987). Epidemiological research has found an increased risk of homicide (Eronen et al., 1996), child abuse (Dinwiddie and Bucholz, 1993), and spousal abuse (Dinwiddie, 1992) in individuals with a diagnosis of ASPD. These individuals often exhibit maladaptive levels of physical aggression, impulsive aggression, and recklessness, in addition to exhibiting higher probabilities of substance abuse (Cadoret et al., 1985; Pajer, 1998; Virkkunen 1979). Individuals with ASPD often have comorbidity with substance use disorders (SUD) (APA, 2000). For example, Regier et al. (1990) conducted a large sample survey of 20, 291 U.S. citizens and found that individuals who meet diagnostic criteria for ASPD, as described by the Diagnostic and Statistical Manuals for Mental Disorders (DSM), were twenty one times more likely to develop abuse/dependence of alcohol than individuals who did not meet DSM criteria for ASPD. Relevant to the goals of this dissertation, individuals with ASPD and a history of SUD are considered to be at the greatest risk for heightened aggressive acts and are more aggressive than ASPD individuals without a history of SUD (Allen et al., 1997).

Additionally, ASPD and SUD individuals generally have higher levels of trait aggression and psychopathic traits (Alcorn III et al., 2013; Allen et al., 1997; Cherek et al., 1997; Moeller et al., 1998; Nouvion et al., 2007). Trait aggression is a psychological construct that describes stable predispositions (i.e., personality traits) that distinguish levels of aggression in ASPD groups from non-ASPD groups (Anderson & Bushman, 2002; Buss & Perry, 1992; Kalome, 2014). Trait aggression can be psychometrically measured and is comprised of subtraits such as anger and hostility, which relate to the affect and cognition of individuals who consistently behave aggressively at above normal rates (Alia-Klien et al., 2009; Buss & Perry, 1992). For example, an individual meeting the diagnostic criteria for ASPD and SUD would likely endorse ratings of irritation when frustrated or feeling as if they are likely to "explode" or be "set off"; which are indices of higher levels of anger. The higher endorsement of experienced anger is an important correlate to aggression. Buss and Perry (1992) described anger as "…a prelude to aggression" (pg 457), as it represents the affective component that drives the transition from thinking about the aggressive act to the actual motor responses in which the aggressive act physically occurs.

ASPD + SUD individuals also have notably higher levels of psychopathic personality traits. It is important to distinguish psychopathic traits from psychopathy. Psychopathic traits refer to constellation of personality traits relating to levels of emotional callousness, interpersonal manipulation, erratic lifestyle, and criminal tendencies that exist on a dimension of high vs low

(Neumann et al., 2012). Psychopathic traits are derived psychometrically from and related to the conceptualization of psychopathy, and are commonly measured by questionnaires. The questionnaires are scored based on the degree to which the person agrees or disagrees with statements relating to their behaviors, beliefs, and personality. Psychopathy is a clinical construct and categorical variable used to describe individuals who are characterized by symptoms of interpersonal dysfunctions, emotional detachment and disinhibited behavior patterns (Anderson & Kiehl, Hare & Neumann, 2008; Kiehl, 2006; 2012). The first person to describe the modern conceptualization of psychopathy was Philippe Pinel in 1801. The concept of psychopathy originates from a group of patients Pinel was overseeing, in which he described their behavior as "*mania san délire*" or "insanity without delirium" (Kiehl, 2006). Pinel's description of these individuals was meant to describe the fact that these patients were disinhibited and unscrupulous, but their behavior could not be attributed to typical mental disturbances such as hallucinations or delusions. Subsequently, Cleckley characterized and delineated the clinical features of psychopaths from both community and institutional settings (Hare & Neumann, 2005; Kiehl, 2006; Hare & Neuman, 2008). Cleckley published his descriptions in the "The Mask of Insanity", which is still used today to characterize psychopaths. From Cleckley's conceptualization of psychopathy, Hare formulized the Psychopathy Checklist (PCL), which was the first clinical instrument introduced in 1980 (later revised in 1991) to separate psychopaths from non-psychopaths (Hare, 1996). Psychopathy is predicative of criminal

recidivism (Hemphill et al., 1998; Leistico, et al., 2008) and is present in 10%-15% of substance abuse populations (Alterman & Cacciola, 1991; Alterman et al., 1993; 1998) and Kiehl (2006) estimated that psychopathy is present in 15-20% of adult inmates in a maximum security prison. Though the construct of psychopathy and the clinical diagnosis of ASPD share common clinical and psychiatric features and similar psychophysiological deficiencies, they are not synonymous (Anderson & Kiehl, 2012; Boccardi et al., 2011; Kiehl, 2006; Patrick, 2014). However, the clinical features of psychopathy as measured by psychopathic personality traits are important in the clinical profile of ASPD+SUD individuals. Alcorn III et al. (2013) found that psychopathic traits were substantially higher in ASPD+SUD individuals versus SUD only individuals and healthy control individuals and, and were major factors in the difference between ASPD+SUD and these two other groups (effect size: $\omega^2 = 0.39$).

Higher trait aggression and psychopathic personality traits have a positive association with the frequency of aggressive behavior, as measured by laboratory tasks of aggression (Alcorn III et al., 2013; Allen et al., 1997; Cherek et al., 1997; Moeller et al., 1997; Nouvion et al., 2007).Thus, individuals who meet diagnostic criteria of ASPD+SUD have aberrant social behavior, affective instability, and poor impulse control. Examining potential therapeutics that might aid clinical efforts aimed at the treatment of maladaptive aggressive behavior in individuals with ASPD +SUD is warranted.

Laboratory task of human aggression: Point Subtraction Aggression Paradigm

The Point Subtraction Aggression Paradigm (PSAP) is a well-established and valid laboratory measure of human state aggression. The utility of the PSAP has been documented in over a dozen studies including acute and chronic drug effects and psychiatric populations (i.e. ASPD and substance abusers) (Cherek et al., 2003). In every study using the PSAP, participants are informed that they will be anonymously paired with another individual (who is actually fictitious) and participants are told that their task is to earn as much money as possible. To achieve this goal, participants are able to utilize three different button options in the PSAP: A, B, and C which correspond to monetarily-reinforced, aggressive, and escape responses, respectively. The A, B, and C Buttons are mutually exclusive response options. Before the participant makes a choice, Buttons A, B, and C are displayed across the computer screen. The first button press response on A, B, or C results in the temporary removal of the other response options from the computer screen until the response requirement on the selected button has been completed. Button A (monetarily-reinforced response) is maintained by reinforcement; the participant gains $0.15 cents upon completion. Button A is on an FR100 (100 presses per $0.15) schedule of responding. The Button B (aggressive response option) in the PSAP is defined as the subtraction of money from the fictitious individual's counter. Completion of Button B (aggressive response option) results in the ostensible loss of $0.15 from the fictitious individual's counter. This is

established by instructional control. Button B is maintained on an FR10 schedule of responding. Aggressive responding on Button B is elicited by provocation; which occurs when a loss of $0.15 from the on-screen counter occurs. These monetary loses (subtractions) are attributed to the fictitious individual paired with the participant. Participants are told that the other (fictitious) individual keeps the money subtracted from the participants' counter (providing an ostensible incentive of the "other person" to use Button B). The participant is informed that money they subtract of the fictitious individual's counter is not added to their own counter. Lastly, completion of Button C (escape response option) responding results in the protection of participant's earnings for a variable interval of time. Button C is maintained on an FR10 schedule of responding. Responding on Button B (aggressive response option) and Button C (escape response option) are maintained by a provocation free interval (PFI). The PFI occurs as a consequence of Button B (aggressive) or Button C (escape) responding, lasts for an average 125 sec ±20%, and allows for suppression of provocations for a variable period of time, which are attributed to the other person. Once the PFI has elapsed, provocations attributed to the other fictitious individual are again presented until more aggressive and escape responding initiates another PFI by using the B or C Button. Participants are not informed about the PFI or its function on Button B. However, participants are informed that Button C protects their earnings from subtractions for a variable period of time. The PFI initiated by Button B (aggressive response) or Button C (escape response) option allows for the

maintenance of the social deception that another person is present, by periodically preventing monetary subtractions.

Laboratory methods of measuring aggressive behavior (such as the PSAP) provide improved precision and manipulation of independent variables - including control over the frequency of the presentation of provocative stimuli compared to data acquired from non-experimental settings. The PSAP shares several important features that allow for the experimental study of aggressive behavior. First, the PSAP provides a social context wherein individuals are engaged in a form of conflict and thus, fits with the psychological constructs of the GAM. Second, aggressive responses are operationally defined as the ostensive deliver of an aversive stimulus (i.e. monetary subtractions), and aggressive responses (Button B presses) are maintained through the temporary cessation of future provocations. Thirdly, the PSAP allows for experimental control of variables influencing aggressive behavior (e.g. frequency of provocation) and is sensitive to pharmacological effects (both acute and chronic). Lastly, physical aggression and violence are sometimes unpredictable, and can be difficult to identify and measure outside of laboratory settings. In addition, experimenters are able to avoid the possibility of physical injury to subjects. Under the conceptualization of the GAM, the PSAP provides a suitable paradigm for the study of aggressive behavior.

Disregulated neurocircuitry in aggression

Conceptually, maladaptive levels of aggression are problem of behavioral self-control (Dawes et al., 1997; Patterson & Newman, 1993). This fundamental problem of self-control over aggressive acts is clinically relevant as repeated levels of aggression that lead to detrimental or aversive outcomes are often diagnostic criteria for psychiatric disorders; in particular, ASPD+ SUD (APA, 2000). Siever (2008) captured this idea in neurobiological terms by suggesting that aggression might be "grounded in an underlying neurological susceptibility". The neural circuitry underlying aggression is likely to be extensive and complex, involving interconnections between several different brain regions. A comprehensive review of all the evidence and brain structures involved in human aggression is beyond the scope of this dissertation. However, are several key brain regions which are believed to subserve human aggression. These regions are the dorsolateral prefrontal cortex (DLPFC), the orbital frontal cortex (OFC), the anterior cingulate cortex (ACC), and the amygdala. These regions are all involved in processing of emotional and social stimuli. Siever (2008) provided an integrative review of how dysregulation of key brain areas give rise to maladaptive aggression in psychiatric populations. Siever (2008) proposed that top down activation in frontal control from the DLPFC, OFC, and ACC are reduced, whereas the amygdala is hyper-responsive to provocation.

These DLPFC-OFC-ACC-amygdala circuits modulate the execution and inhibition of aggressive acts (Siever, 2008). Dysregulation of this circuitry

disrupts self-control in the presence of provoking stimuli. Several converging lines of evidence support the hypothesis of reduced frontal functioning and over-responsive amygdala drive underlying maladaptive aggressive behavior (Bufkin & Luttrell, 2005; Coccaro et al., 2011; Davidson et al., 2000; Siever, 2008). Non-human primates with experimentally induced lesions in the dorsolateral prefrontal cortex (DLPFC) and the orbital frontal cortex (OFC), reliably show increased aggressive behavior (Butter et al., 1970; Raleigh et al., 1979). Structural and functional imaging in individuals with a history of physical aggression and/or violent acts has revealed evidence for cortical thinning and volume reduction, reduced cerebral blood flow, and reduced baseline brain metabolism in these regions (e.g., DLPFC, OFC, and ACC) (Coccaro et al., 2011; Goyer et al. 1994; Raine et al., 1997, Raine et al., 1998a; 1998b; Volkow et al., 1995). Substantial evidence for limbic hyper-responsiveness comes from patients with borderline personal disorder (BPD); an Axis-II psychiatric personality disorder that has many clinical features similar to ASPD. Psychophysiological and functional neuroimaging studies have demonstrated that when individuals with BPD are exposed to negatively-valenced stimuli (e.g. faces with negative emotion or traumatic stimuli) the amygdala shows hyperactivation (Donegan et al., 2003; Herpetz et al., 2001; Koenigsberg et al., 2007; Minzenberg et al., 2007; Schmahl et al., 2004). In pre-clinical studies, direct electrical stimulation of the cortiomedial amygdala of male Syrian hamsters decreased the latency of attack behaviors, indicating an increase in aggressive arousal by amygdala stimulation (Potegal et al., 1996).

Neuroimaging studies examining affective dysregulation in psychiatric populations provide further evidence that maladaptive aggression arises from both reduced frontal activation and over-responsive limbic activation. Boccardi et al. (2011) found volumetric reductions in the gray matter of the ACC and OFC, and tissue enlargement of the central and lateral nucleus of the amygdala in male psychopaths with a SUD, compared to age-matched male controls. Boccardi et al. (2011) described reduction in cortical gray matter in the ACC and OFC as being in concert with studies using functional magnetic resonance imagining (fMRI) and laboratory paradigms in psychopaths; indicating that the structural differences in psychopaths with SUD, compared to controls, reflect poor maintenance of cognitive and emotional processing and poor processing of information about societal rules. Boccardi et al. (2011) also noted that the enlargement of the central and lateral nucleus of the amygdala of psychopaths could be related to "…increased propensity of offenders for impulsive aggression, abnormal motivation processes, and reduced sensitivity to stress" (pg 90). Albein-Urios et al. (2013) utilized fMRI to measure the blood oxygenated level dependent (BOLD) signal of cocaine dependent individuals with comorbid cluster B personality disorders (e.g., ASPD) during a paradigm of negative emotion appraisal and maintenance, and found that the BOLD signal was reduced in the ACC compared to cocaine dependent-only and healthy controls. This outcome is indicative of dysfunctional decision making about social behavior. These deficiencies are prevalent in cocaine dependent and personality disordered individuals. Additionally, Albein-Urios et al. (2013)

found that the BOLD signal in the amygdala was positively correlated to antisocial-related cognitive beliefs and negative urgency (e.g., strong impulses under negative affect). Data from Albein-Urios et al. (2013) indicate that personality disordered and SUD individuals have deficiencies related to the experience of aversive states, which is important for understanding the dysregulated neurocircuitry of maladaptive aggression.

Psychopharmacology of aggression: Serotonin, GABA, Testosterone

The central nervous system (CNS) evolved to process information about signals from the environment. The process by which environmental signals are transmitted between synapses is called neurotransmission and the molecules which transmit these signals are called neurotransmitters. Another class of signaling molecules is called hormones. Hormones communicate signals between organs and tissue. Decades of psychopharmacological research have identified two chief neurotransmitter systems which are thought to regulate aggression: serotonin (5-hydroxytrotamine, 5-HT) and gamma-aminobutyric-acid (GABA) (Coccaro et al., 2011; de Almeida et al., 2005; Krakowski, 2003; Miczek et al., 2002; Miczek et al., 2004a, 2004b; Moore et al., 2002) The major hormone that is hypothesized to modulate aggression across different animal species is testosterone (Archer, 2004; Soma, 2006).

Serotonin and aggression

The major role of the 5-HT neurotransmitter system in the regulation of aggressive behavior is to inhibit aggressive responses, specifically impulsive aggressive responses (Coccaro et al., 2011; Miczek et al., 2002). The most notable consistent evidence for the association of central actions of 5-HT and aggressive behaviors in humans is that cerebral spinal fluid (CSF) levels of the 5-HT metabolite 5-hydroxy indolacetic acid (5-HIAA), a marker of 5-HT activity, in the CSF are inversely correlated with aggressive behavior (Moore et al., 2002; Krakowski, 2003). This inverse correlation has been found in populations with heightened aggressive behavior (Coccaro, 1998; Placidi et al., 2001) including violent offenders (Brown et al., 1979; Linnoila et al. 1983). Moore et al. (2002) conducted meta-analysis of studies examining this inverse relationship between CSF levels of 5-HIAA and antisocial behavior spanning 25 years and found a moderate effect size (Cohen's d = -0.45). The CSF levels of 5-HIAA in antisocial groups were approximately one half of one standard deviation below control comparison groups. Lower levels of 5HIAA in CSF are indicative of low serotonergic activity in the brain (Krakowski, 2003). Evidence from animal literature further supports the negative association between low 5-HT activity and aggressive behavior. In rats that have had their central levels of 5-HIAA experimentally reduced via tryptophan depletion, the rate of mouse killing behavior increases (Gibbons et al., 1979). Further, destruction of serotonergic neurons in the raphe nucleus of rats increases the rate of mouse killing behavior and this effect is reversed by the administration of serotonergic-

mimetics (Molina et al., 1987). In non-human primates, low CSF levels of 5-HIAA are associated with severe aggression and impaired impulse control (Higley et al., 1992; Mehlman et al., 1994) in both males (Higley et al., 1996a) and females (Higley et al. 1996b). Evidence from human psychopharmacological studies also supports an inverse relationship between serotonergic activity and aggressive behavior. Acute (Cherek & Lane, 1999, 2001) and chronic administration (Cherek et al., 2002a) of 5-HT agonists that block the reuptake of 5-HT decrease the aggressive behavior of individuals with a history of Conduct Disorder (CD). Gowin et al (2010) found that acute administration of zolmitriptan, an agonist for the $5\text{-HT}_{1B/D}$ receptor, attenuates aggressive behavior under the influence of alcohol. Conversely, aggressive behavior on the PSAP increases following depletion of tryptophan, the rate limiting enzyme for 5-HT synthesis, most prominently in individuals who have high baseline levels of aggression on the PSAP (Moeller et al., 1996; Bjork et al., 1999, 2000).

The inverse association between serotonergic activity and aggression is well studied, but until recently a drawback was the fact that investigators did not know precisely where in the human brain these serotonergic effects might be occurring. Passamonti et al. (2012) experimentally decreased the levels of 5-HT though acute tryptophan depletion in healthy individuals and subsequently scanned these individuals using fMRI during the viewing of angry versus sad and neutral faces. The presentation of an angry face is an ecologically valid method of examining the neural correlates of reactivity to threats, as an angry

face is an aversive stimulus which signals social threat (Green & Phillips, 2004). Passamonti et al. (2012) found when viewing angry versus neutral and angry versus sad faces, acute tryptophan depletion in healthy volunteers reduced the functional connectivity between the amygdala and PFC, specifically in the ventral ACC and ventral lateral PFC. Thus, the actions of 5-HT modulating aggressive behavior occur within the same brain regions which subserve human aggression. Though the neurotransmitter 5-HT is a major neuromodulator of aggression, it is not the only neurotransmitter with known pharmacological effects on aggression.

GABA and aggression

The neurotransmitter GABA is the major inhibitory neurotransmitter in the CNS and GABAergic containing neurons are widely spread across the brain. The dose-response function across different GABAergic agents and aggressive behavior is non-linear. GABAergic agents are capable of either increasing or decreasing aggressive behavior in some contexts and at certain doses (Miczek et al., 2002). For example, several benzodiazepines (chlordiazepoxide, diazepam, and midazolam) have “bitonic effects” on aggressive behavior. The bitonic effects of these benzodiazepines refer to the pattern of increasing aggressive behavior at low doses while decreasing aggressive behavior at high doses (DiMascio et al., 1973; Miczek et al., 2002). These bitonic effects on aggressive behavior are not only found in humans but also mice, rats, pigs, and monkeys (Miczek et al., 2002).

Certain GABAergic agents have been shown to decrease aggressive behavior. Both acute and chronic administration of the anticonvulsant tiagabine (which increases the level of GABA at the synapse by blocking the reuptake of GABA) decreased the frequency of aggressive responding on the PSAP in antisocial and substance abuse populations (Gowin et al., 2012; Lieving et al., 2008). In individuals with a history of CD, acute administration of the anticonvulsant gabapentin decreased the frequency of aggressive responding as measured by the PSAP at highest dose (800 mg), but increased the frequency of aggressive responding at lower doses (200 mg and 400 mg) (Cherek et al., 2004).

Certain GABAergic agents have been shown to increase aggressive behavior. Positive allosteric modulators of the $GABA_A$ receptor complex provide the most compelling evidence of the aggression-heightening effects of GABAergic agents (de Almeida et al., 2005; Heinz et al., 201; Miczek et al., 2002, 2004). The most well-established psychoactive compound that is active at the $GABA_A$ receptor complex and has aggression heightening effects is alcohol (for reviews see Miczek et al., 2002, 2004; Hienz, 2011). Experimental models in both humans and animals have consistently shown increases in aggressive behavior following alcohol consumption, particularly at low to moderate doses (Miczek et al., 2004; Heinz, 2011). Germane to this dissertation, a study conducted by Moeller et al (1998) found that ASPD individuals showed significantly greater increases in the frequency of aggressive responding on the PSAP under alcohol compared to non-ASPD

individuals. Moeller et al. (1998) attributed the ASPD findings to the effect of alcohol on reducing frontal lobe functioning, and evidence from neuropsychological tests that antisocial populations have reduced frontal cortex functioning, thereby increasing the susceptibility of ASPD individuals to the effects of alcohol.

Testosterone and aggression

Another neuromodulator regulating aggression is testosterone. Kouri et al. (1995) provided the experimental evidence for the aggression increasing effect of testosterone in humans. Kouri et al. (1995) found that chronic administration of testosterone increases the frequency of aggressive responding on the PSAP in healthy male volunteers. A hypothesis on the association between circulating levels of testosterone and aggression is the "Challenge Hypothesis" (Wingfield et al., 1990). The Challenge Hypothesis describes the association between changes in testosterone in relation to intermale aggression in songbirds during mating seasons. Wingfield et al. (1990) posited that an increase in the levels of plasma testosterone in songbirds was beneficial to reproduction strategies by engendering mate guarding and preventing the encroachment of sexual rivals. Support for the Challenge Hypothesis is found in a variety of vertebrate species including songbirds and sparrows (Soma, 2006; Wingfield et al., 1990), cichlid fish (Hirschenhauser et al., 2004), chimpanzees (Muller & Wrangham, 2004) and humans (Archer, 2004). The Challenge Hypothesis explains the association

between physiological changes in testosterone and aggressive behavior as a cost-benefit ratio for maximizing reproductive success. The “Biosocial Model of Status” (Mazur, 1985) is another model that explains the association between physiological levels of testosterone and aggression. This model is based on a series of situations wherein a primate’s level of testosterone varied as a function of competition outcomes. Specifically, winners of competitive outcomes show an increase in the level of circulating testosterone and losers of competitive outcome show a decrease in their levels of circulating testosterone. Mazur (1985) further proposed that competitive outcomes challenge a primate’s dominance status and testosterone levels increase and promote aggressive behavior in primates as a means of protecting their status. The Challenge Hypothesis and the Biosocial Model of Status both predict that circulating levels of testosterone promote aggressive behavior in response to current and/or future outcomes, in accord with changes in the environment (Mazur, 1985; Wingfield et al., 1990). Support for this prediction in humans comes from studies by Carre´et al. utilizing the PSAP methodology to examine the association between circulating levels of testosterone and human aggressive behavior. Carre´& McCormick (2008) and Carre´ et al. (2010) demonstrated that increases from the baseline concentration of circulating testosterone were positively correlated with increases in aggressive behavior on the PSAP. Carre´ et al. (2009) found that in men who had higher psychometric scores of trait dominance, increased aggressive behavior on the PSAP was observed following victory on a competitive task. Additionally, increases from the baseline

concentration of circulating testosterone were also observed in these men following a victory.

In general, increased circulating levels of testosterone are associated are increased aggression. Within clinical contexts, in groups with psychopathologies there appears to be a positive association between circulating levels of testosterone and maladaptive aggression as well as violent behavior. Dabbs et al. (1995) studied 692 inmates and found that higher plasma levels of testosterone were positively associated with violent criminal charges. Charges for rape, homicide, and robbery were respectively, 3.6, 2.1, and 1.5 times more prevalent in inmates with higher levels of testosterone as compared to inmates with lower levels of testosterone. Reviews by Yildirim & Dersken (2012a, 2012b) found that high circulating levels of testosterone are a risk factor for interpersonal and affective deficits and lifelong antisocial behavior in psychopathic males.

Summary

The neurochemistry of aggression has been studied in several species. Modulation of aggressive behavior involves alterations in neurotransmission, chiefly the signal transmission from serotonergic, GABAergic, and testosterone systems in the CNS. Currently, there are no approved medications from the Food and Drug Administration (FDA) for the treatment and management of aggressive behavior (Newman, 2012). Currently, no medication has been indicated for the management of aggressive behavior in ASPD and/or SUD

individuals (Newman, 2012). Thus, exploration into drug discovery and psychopharmacological management of aggression for ASPD +SUD are warranted. In recent years, neuropeptides and neuropeptide systems have become research targets for treating deficits in the social behavior of psychiatric populations (Meyer-Lindenberg et al., 2011; Meyer-Lindenberg & Tost, 2012). One neuropeptide of much recent interest is oxytocin (OT). The neuropeptide OT and its effect on aggressive/social behavior was the focus of the experiments in this dissertation.

Scientific and clinical relevance: Oxytocin and the oxytonergic system

The neuropeptide OT is a hormone produced in the magnocellular neurons in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus (Carter, 2003; Gimpl & Fahrenholz, 2001). Axonal projections from OT-containing neurons in the PVN reach many brain regions that are important for modulating social behavior, such as the amygdala, nucleus accumbens, and frontal cortices (Bethlehem et al., 2013; Meyer-Lindenberg et al., 201; Ross et al., 2009; Young et al., 2005) (Figure I.B) . Release of OT from neural tissue is accomplished via volume transmission, as OT is released form the soma, axon, and dendrites (Ludwg & Leng, 2006; Neumann & Landgraf, 2012). OT is a nonapeptide and the structure of OT is highly conserved across many animal species (Gimpl & Fahrenholz, 2001

; Lee et al., 2011; Koehbach et al., 2013). The release of OT into general circulation is achieved by coordinated action from the brain and posterior pituitary (Ludwig & Leng, 2006; Neumann & Landgraf, 2012). Free circulating OT can bind to its receptor. Only one receptor for OT has been discovered and characterized (Gimpl & Fahrenholz, 2001). The OT receptor is a seven transmembrane receptor channel rhodopsin-type G-protein ($G_{\alpha q11}$) coupled receptor coupled to phospholipase C, and is present in central and peripheral neural tissue (Ebstein et al., 2012; Gimpl & Fahrenholz, 2001).

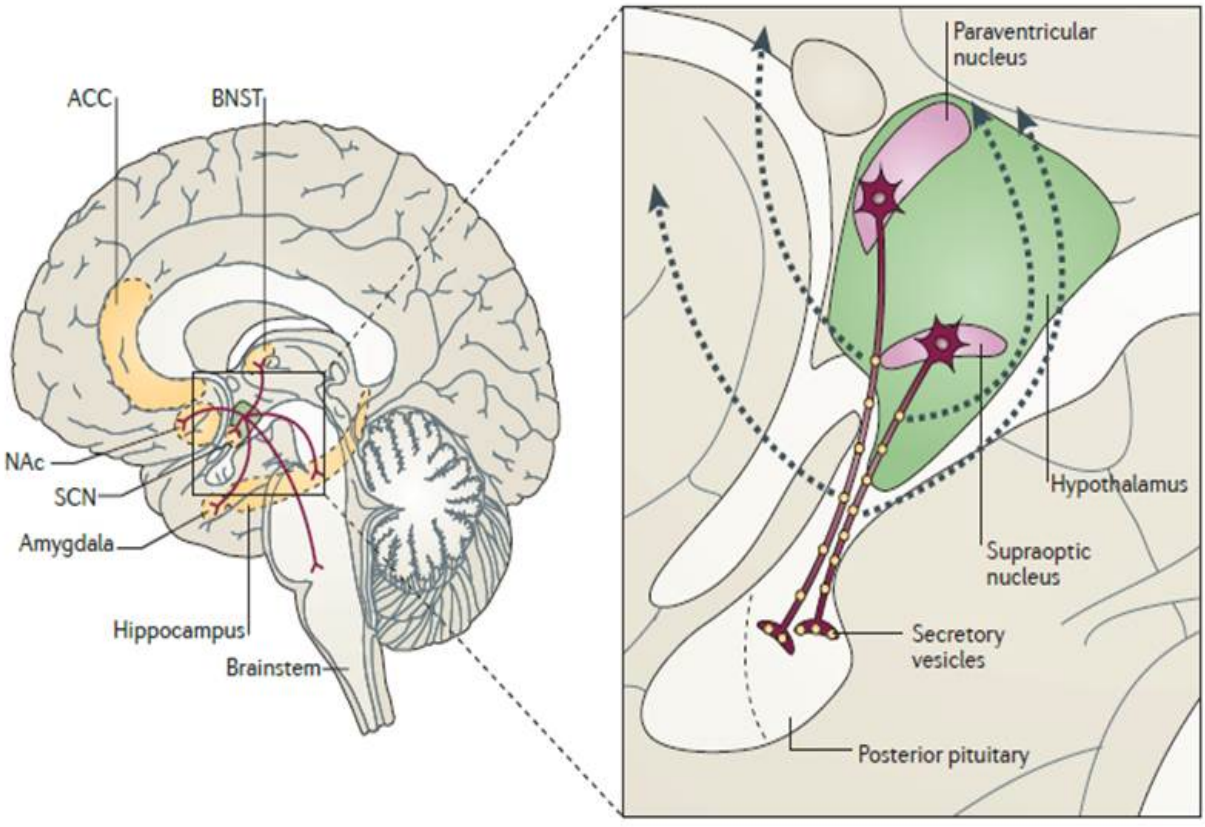


Figure I.B Axonal projections from OT containing neurons in the PVN and SCN of the hypothalamus. Anterior cingulate Cortex, (ACC), Bed Nucleus of Stria Terminalis (BNST), Nucleus Accumbens (NAc). Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nature Reviews Neuroscience. 12, 524-538 (September 2011); Permission 3491511505185, Nature Publishing Group)

Historically the neuropharmacological actions of OT were focused on lactation and birth (Carter, 1992; Gimpl & Fahrenholz, 2001). Across rodent, sheep, and primate species, OT promotes sexual behavior in both males and females, and mammalian maternal behavior (Carter, 1992; Carter et al., 1995; Carter, 2008). Given that OT demonstrated critical roles in mammalian sexual and maternal behaviors, several subsequent studies hypothesized that OT is critically important for mammalian social monogamy and social bonds (Carter, 1992; Carter et al., 1995). Indeed, the past four decades of research have demonstrated that the oxytonergic system is critically involved in regulating and modulating social behavior in the forms of increased social contact, formation of partner preferences, and autogrooming of partners (Ahern et al., 2009; Carter et al., 1995; Carter, 2014; Donald & Young, 2008; Kiss & Mikkelsen, 2005; Lee et al., 2009a; Meyer-Lindenberg et al., 2011). The most well-known animal species, from which much of the scientific knowledge about the OT system in relation to mammalian social monogamy and social behavior is grounded, is the prairie vole. Prairie voles are monogamous rodents found in the Great Plains of North America that form lifelong partnerships following mating called pair bonds (Williams et al., 1992) and the formation of these pair bonds is dependent on OT (Williams et al., 1994). The administration of OT in the formation of pair

bonds in prairie voles was a critical discovery in the field of social behavior. Young (2009) stated “There is intriguing overlap between the brain areas involved in vole pair bonding and those associated with human love” (pg 148). Since the OT system is conserved across mammalian species, the OT system in humans may have evolved because it is advantageous for humans to form social bonds and engage in mutually beneficial (or prosocial) interaction (Carter, 2002; Carter, 2003; Rilling & Sanfey, 2010). Studies of intranasal OT dosing and human social behavior and socio-emotional cognition in psychiatric disorders lend support this notion.

Oxytocin research: human social behavior

In humans, the OT system promotes the occurrence of prosocial behaviors. Several studies have established that OT administration increases behaviors of cooperation, trust, and generosity following acute administration (Baumgartner et al., 2008; Kosfeld et al., 2005; Rilling et al., 2012; Zak et al., 2007). Most studies involving acute OT dosing have utilized paradigms from behavioral economics. These paradigms can quantitatively measure human social behavior. In these paradigms, participants engage in behaviors that may be operationally defined as prosocial or antisocial. Two important examples of prosocial behaviors are trust and generosity. Kosfeld et al. (2005) utilized an economic paradigm which measured monetary transfers between investors and trustees. This paradigm is called the “Trust Game” in which, investors may transfer monetary amounts to trustees who may choose to share the proceeds

given to them or may keep the entire amount. Kosfeld et al. (2005) parametrically manipulated the amount investors could give to trustees and found that investors who were given OT made more transfers containing higher monetary amounts to trustees, compared to investors who were given placebo. Additionally, when provided the opportunity to give the trustee the maximal monetary amount possible, 45% of the investors who were given OT chose to transfer the maximal amount. Zak et al. (2007) conducted a behavioral economic study in which participants assigned to either the OT or placebo group and were given $10. All participants were provided the opportunity to split the money with a stranger in a one shot decision. More money given to the stranger represented more generosity by the participant. Zak et al. (2007) observed that participants who were administered OT were 80% more generous than participants given placebo.

A prosocial behavior germane to this dissertation is cooperation. Behavior economic paradigms have shown instances in which OT dosing increases cooperation (De Dreu et al., 2010; Rilling et al., 2012). Human cooperation has been defined as reciprocal exchange which can lead to an immediate mutual benefit or gain (Camerer, 2003; Rilling & Sanfey, 2010). Human cooperation falls broadly under the domain of altruism (acts that result in economic benefits to another individual or individuals), which is common in human societies (Fehr & Fischbacher, 2003; Rachlin & Locey, 2011). Human cooperation has been suggested as an evolutionary mechanism and a form of self-control because the long-term benefits of cooperation outweigh the long-

term costs (Rachlin & Locey, 2011). A behavioral economic paradigm called the Prisoner's Dilemma (PD) arranges social interactions between two partners in which choices can result in monetary gain or losses for both individuals. In a standard PD game human participants select between two response options: a cooperative response and a noncooperative response (sometimes referred to as defection). The interaction of these two response options: lead to monetary payoffs. Specifically, the cooperative response option results in equal mutual monetary gain for both partners, whereas the noncooperative response option either maximizes individual gain to one person and loss to the other, or results in loss to both people. Under most situations, mutua cooperative responses are selected approximately 50% of the time between two partners (Camerer, 2003; Rilling & Sanfey, 2011). Over repeated trials, most people adopt a tit-for-tat strategy in reciprocating cooperation following trials of mutual cooperation (Camerer, 2003; Fehr & Fischbacher, 2003; Rachlin & Locey, 2011). In studies using the PD, OT dosing produced increased rates of cooperative responding following both cooperation and defection from the other paired partner (Rilling et al., 2012) and within group cooperation during a multiplayer PD (De Dreu et al., 2010).

The collective evidence that OT increases cooperative behavior is pertinent to the goals of this dissertation and gives rationale for investigating aggression in ASPD+SUD. Alcorn III et al. (2013) reported that psychopathic and aggressive personality traits are two important clinical features that distinguish ASPD+SUD individuals from SUD only and healthy volunteers. In

the context of social behavior, Alcorn III et al. (2013) findings are relevant to the dissertation hypothesis, as individuals with psychopathic traits have higher instances of noncooperation (antisocial behavior) on the PD task (Mokros et al., 2008; Rilling et al., 2007). Rilling et al., (2007) found that individuals with higher psychopathic personality traits show less cooperative responding (pearson's r correlation: r = -0.58) and lower likelihood to cooperate after mutual cooperation (pearson's r correlation: r = -0.64) (Rilling et al., 2007). Mokros et al. (2008) found that psychopathic individuals with a criminal history residing within a high security psychiatric forensic institution were more likely to choose a noncooperative response option (only seeking to maximize individual gain) compared to healthy adult volunteers when engaged in PD.

Across several studies, OT engendered increases in prosocial behavior. Psychopathic traits are characterized, in part, by antisocial behavior. These traits are prevalent in ASPD+SUD. It follows, therefore, that OT should reduce antisocial behaviors such as aggression in those for whom it is exaggerated (e.g., ASPD and SUD). Interestingly, Lee et al. (2009b) found that in persons with personality disorders (e.g. ASPD) CSF levels of OT were significantly inversely correlated with a lifetime of aggression (pearson's r correlation: r = -0.33), suggesting central signaling of OT. Additionally, individual differences in the OT system have been associated with maladaptive behavior. For example, polymorphisms in OT receptor genes have been related to extreme, persistent aggressive behavior during childhood (Malik et al., 2012). Mizcek et al. (2002)

and Siever (2008) both suggest that OT contributes to the control of mammalian and human aggression.

The potential of OT as a therapeutic for impulsive aggression has not been tested. However, the idea that OT could be used in psychiatric disorders has been gaining support (Meyer-Lindenberg et al., 2011). The neuropeptide OT facilitates social cognition in individuals with disorders characterized by deficits in social behavior and social cognition. Administration of OT increased the inference of emotional states of others and empathic accuracy in individuals with autism-spectrum disorders (Domes et al., 2007a; Guastella et al., 2010); increased emotional recognition in patients with Schizophrenia (Averbeck et al. 2012); and reduced neuropsychiatric scores of agitation, dysphoria, and irritability in patients with frontotemporal-dementia (Jesso et al., 2011). These data provide support for the examination of OT in modulating aggressive behavior.

Hypotheses and aims

There is evidence for the therapeutic potential of OT on social behavior and socio-emotional processing in psychiatric disorders. There are no FDA approved medications for the treatment of aggression in ASPD+SUD (Newman, 2012). Substantial work has shown that OT increases prosocial behavior in both humans and nonhuman animal species. The converging evidence suggests that administration of OT should reduce aggressive behavior in humans and is a potential therapeutic target for psychiatric disorders, particularly ASPD+SUD. The overall hypothesis of this dissertation is that OT administration will decrease human aggressive behavior vs placebo.

Experiment 1

Aim 1a: To test if OT administration decreases aggressive responding in ASPD+SUD individuals

Hypothesis 1a: Compared to placebo, acute OT administration will dose-dependently decrease aggressive behavior in ASPD+SUD individuals (48 IU > 24 IU > 12 IU > placebo).

Experiment 2

Aim 2a: To test if acute OT dose (24 IU) decreases aggressive behavior.

Hypothesis 2a: Healthy adult male participants will show reduced aggressive responding following OT administration, as compared to placebo.

Aim 2b: To explore if interpersonal manipulation and anger personality traits are correlated with aggressive behavior under OT dose (24 IU).

Hypothesis 2b: There will be a negative association between psychometric scores of interpersonal manipulation and anger and aggressive responding under OT dosing.

Aim 2c: To test if acute OT dose (24 IU) changes social judgment following an aggressive encounter.

Hypothesis 2c: Healthy adult male participants will have increased ratings of likability of the "other person" under OT, as compared to placebo.

CHAPTER 2: EFFECTS OF INTRANASAL OXYTOCIN ON AGGRESSIVE RESPONDING IN ANTISOCIAL PERSONALITY DISORDER AND SUBSTANCE USE DISORDER

Portions of the work presented here are taken from Alcorn III, J.L., Rathnayaka, N., Swann, A.C, Moeller, F.G., & Lane, S.D. “Intranasal Oxytocin on Aggressive Responding in Antisocial Personality Disorder” (In Press) The Psychological Record.

Introduction

Human social interaction involves complex and dynamic behavior patterns. One enduring and problematic form of social behavior is aggression. Aggression can be defined as the presentation of an aversive stimulus by one individual to another individual who finds the aversive stimulus harmful and would seek to avoid it (Baron & Richardson, 1994). The consequences of aggression present considerable burdens on public health, criminal justice systems, and communities (Arseneault et al., 2000; Kessler, et al., 2006; Rasmussen & Levander, 1996). Aggressive behavior is often heightened in individuals with Antisocial Personality Disorder (ASPD) and a history of substance use disorders (Alcorn III et al., 2013; Allen et al., 1997; Bjork et al, 1999; Cherek et al., 1997; Cherek & Lane, 1999). Examination of behavioral and pharmacological modifiers of aggression in these high-risk individuals is of interest to scientific, therapeutic and public health endeavors (Patrick, 2008; Siever, 2008; Takahashi et al., 2012).

In the search for effective interventions aimed at improving the social functioning of individuals with psychiatric disorders, the neuropeptide oxytocin (OT) and the oxytocinergic system may hold promise as an intervention

strategy for promoting prosocial behaviors (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). OT is primarily synthesized in the nuclei of the hypothalamus (Lee et al., 2009a; Ludwig & Leng, 2006). Oxytocinergic axonal projections from the hypothalamus reach the prefrontal cortices, amygdala, and nucleus accumbens, which are important in modulating social behavior in human and nonhuman animals (Gimpl & Farhenholz, 2001; Lee et al., 2009a; Meyer-Lindenberg et al., 2011). OT administration increased prosocial behaviors of cooperation, trust, and generosity following acute administration to healthy adult humans (Baumgartner et al., 2008; Kosfeld et al., 2005; Rilling et al., 2012; Zak et al., 2007). The prosocial effects of OT dosing in nonhuman animal studies suggest that this system underpins affiliative behaviors in both the social-bonds of monogamous rodents (Young et al., 2011) and parental behavior of rodents and primates (Febo et al., 2005; Saltzman & Maestripieri, 2011).

In recent studies, OT was shown to facilitate social behavior in individuals with disorders characterized by deficits in social behavior and cognition (e.g. autism-spectrum disorders, frontotemporal-dementia, and schizophrenia) (Meyer-Lindenberg et al., 2011). Conversely, polymorphisms in OT receptor genes have been associated with extreme, persistent aggressive behavior during childhood (Malik et al., 2012). To date, only one study has examined the potential impact of OT on human aggressive behavior. Campbell & Hausmann (2013) found evidence to suggest that OT administration might reduce aggressive behavior in women with high state anxiety. However,

Campbell & Hausmann (2013) conducted a between groups design that used healthy women volunteers who were tested at one OT dose level and no main effect of dose was observed. Given the reported prosocial effects of OT on the social behavior of rodents, primates, healthy adults, and individuals with diagnosed psychiatric disorders, this experiment sought to examine the potential impact of OT on aggressive behavior in individuals with ASPD and past substance use disorders. This combination of comorbidities represents the highest risk for violence and aggression (Alcorn III et al., 2013; Arseneault et al., 2000; Kessler et al., 2006; Rasmussen & Levander, 1996).

This experiment was the first placebo-controlled study using a well-established operant laboratory measure of human aggression (Point Subtraction Aggression Paradigm, PSAP) across a range of doses (12, 24, and 48 International Units, IU) to examine changes in aggressive responding under OT dose. The hypothesis of this experiment was that OT would dose-dependently decrease aggressive responding compared to placebo.

Materials and Methods

All experimental procedures were reviewed and approved by the Institutional Review Board for the University of Texas Health Science Center-Houston, USA. Prior to study participation, informed consent was obtained from all participants.

Participants

Six adult males were recruited into the study via newspaper advertisements seeking male individuals on parole or probation. Newspaper advertisements were placed in freely distributed papers in the Houston metropolitan area. Individuals on parole or probation were recruited because the incidences of comorbid ASPD, past SUD and heightened aggressive are over represented in this population. Prior to study participation all participants underwent a physical exam to screen for exclusionary medical conditions (e.g. HIV, seizures, cardiovascular, kidney or endocrine diseases, diabetes, high blood pressure, and history of head trauma or loss of consciousness > 20 minutes) and current use of prescription medication. Female participants were excluded for the following reasons: (i) the male to female ratio for ASPD is 9 to 1, respectively (APA, 2000), thus female participants would be not representative of the target populations desired in this study, (ii) the neuropeptide oxytocin increases levels of luteinizing hormone (Evans et al., 2003) which could potentially affect the regularly occurring menstrual cycles of female participants, and (iii) there are no reports of the interactions of oxytocin administration with oral contraceptives (i.e. birth control), thus behavioral and physiological side effects are unknown. Therefore, females were not recruited for both scientific and safety reasons.

Prior to study participation all participants underwent screening for current and past psychiatric illness using the Structured Clinical Interview of the

DSM-IV (SCID) (First et al., 1996) and the SCID-II NP (Personality Disorders; First et al., 1997). The SCID-I and SCID-II were administered by a trained mental health professional. The SCID was used to screen for Axis I disorders and determine that participants met DSM-IV criteria for past SUD. Participants were excluded if they met DSM criteria for Axis I disorders other than past SUD. The SCID-II was used to ascertain that all participants met criteria for ASPD (i.e. childhood conduct disorder by age 15 and ASPD in adulthood). General cognitive capacity was assessed using The Shipley Institute of Living Scale-2 (Shipley et al., 2009) a test of general cognitive aptitude consisting of a 40-item vocabulary test and a 26-item block test. Average composite verbal and block score on the Shipley-II was 176.16 (SD = ± 20.6: age-adjusted normative percentile with a Weschler Adult Intelligence Scale estimated mean of 86). All six participants were within two standard deviations of the Shipley-II normed means and had 12 or less years of education (range 9-12, see Table 1.A)

Participant	Age	Years of Education	Criminal History	Past SUDs
s13121	37	12	aggravated assault, drug possession, theft	a,b,e
s13146	24	9	burglary parole/probation violation charge	b
s13214	51	12	Burglary	a,b
s13234	27	11	Parole/probation violation	a,c,d,g,h
s13246	28	12	drug possession	b,d,g,h
s13285	46	11	aggravated assault	a,b,c,h

Table 1.A Participant demographics. Participant age, years of education, criminal history, and past substance use disorder (SUD) are presented. All six subjects met Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for Antisocial Personality Disorder. All participant demographic data were collected using the Structured Clinical Interview of the DSM-IV (SCID-I and SCID-II, personality disorders). Past SUDs (dependence) are coded as following: a= alcohol; b= cannabis; c= cocaine; d= hallucinogen; e= inhalant; g= opiate; h= sedative.
Taken from Alcorn III et al. (In Press).

To avoid potential interactions between OT and extraneous drug use and alcohol intoxication during study participation, participants with any current SUD were excluded, and all participants had to provide clean urine and expire breath samples on testing days. Urine samples were screened for extraneous drugs using the Enzyme Multiple Immunoassay Technique Drug Abuse Urine Assay (Innovacon; San Diego, CA). Two positive detections were recorded during this study; one participant was positive for cannabis and another participant was positive for cocaine. Both participants were precluded from study participation until negative urine samples were obtained the following experimental day. Expired breath samples were collected each morning of testing to detect alcohol consumption.

Apparatus

Participants were seated in a 1.2m X 1.8m sound-attenuated testing room containing a video graph array (VGA) monitor and a 19cm X 43cm X 25cm USB-connected response panel containing four colored buttons (blue, yellow, green, and red). The blue, yellow, and green buttons represented the 'A', 'B', and 'C' response options displayed on the VGA monitor, respectively. The red button had no programmed consequence. The VGA monitor and response device were linked to Pentium-based computer located outside of the testing room which controlled and recorded all experimental sessions.

Procedure

The Point Subtraction Aggression Paradigm (PSAP) is a well-established and validated laboratory measure of human state aggression. The utility of the PSAP has been documented across many studies, with demonstrated sensitivity to acute drug administration (Lane & Cherek, 2000) and aggressive response patterns in psychiatric populations, including ASPD and substance abuse (Allen et al., 1997; Bjork et al., 1999; Cherek et al., 1997; Cherek & Lane, 1999; Cherek et al., 2003). Participants were informed that they would be anonymously paired with another individual (who was actually fictitious) and participants were told that their task was to earn as much money as possible. To achieve this goal, participants were able to utilize three different button options labeled A, B, and C which correspond to monetarily-reinforced, aggressive, and escape responses, respectively. The A, B, and C Buttons were non-reversible response options. Before the participant made a choice, Buttons A, B, and C were displayed across screen on the VGA monitor. The first response on A, B, or C resulted in the temporary removal of the other response options from the computer screen until the selected response option requirement was completed. Button A (monetarily-reinforced response) was maintained on an FR100 (100 presses) schedule of responding. The participant gained $0.15 cents for each completed FR100 on button A. Completion of Button B (aggressive response) responding resulted in the ostensible loss of $0.15 from the fictitious other person's counter. In accord with the operational

definition of aggression, the aggressive response option is defined as the ostensible subtraction of money from the fictitious individual's counter. Button B (the aggressive response) was maintained on an FR10 schedule of responding. Aggressive responding was elicited by provocation; which occurred probabilistically on average every 125 sec ± 20% and resulted in a loss of $0.15 from the participant's counter. These monetary loses (subtractions) were attributed to the fictitious individual paired with the participant. Participants were told that the other (fictitious) individual kept the money subtracted from the subject's counter. The participant was informed that money he subtracts from the fictitious individual's counter is not added to his own. Thus, the aggressive option was not maintained by monetary gain. Completion of Button C (FR10; escape response) responding resulted in the protection of subject's earnings for a variable interval of time (a provocation-free interval averaging 125 sec ± 20%). Because both Button B (aggressive response) and Button C (escape response) option produce a provocation-free interval, they also provide support for the social deception that another person is present by reducing (but not preventing) subtractions throughout the PSAP sessions. In the present study, responding on Button C was not analyzed as because not all participants used Button C and those that did, did so sparingly. To establish all PSAP contingencies and the social context, participants read a printed set of instructions describing the response requirements for all three response options and consequences on each option (the instructions only attribute the provocation free interval to Button C). If the participant asked questions

pertaining to the PSAP, the instructions were repeated verbally from the printed instructions and clarified by a trained research assistant. Each study day, participants had completed four PSAP sessions at 30min, 90min, 150min, and 210min post dose (Session 1, 2, 3, and 4, respectively). Each PSAP session lasted 25min. One participant (s13825) did not complete a PSAP 210min post dose. At the end of each experimental day, participants completed a short open-ended questionnaire to assess the veracity of the instructional deception in the PSAP. All participants reported being paired with another individual on every experimental day.

Drug administration

Dose order was counterbalanced across all six participants. Prior to dose administration, all participants were trained on the dosing procedures using 1.5ml of saline to ensure accurate were administration and comfort with the drug administration procedures. Participants were administered intranasal doses (12, 24, and 48 IU) of synthetic OT (Syntocinon, nasal spray: Novartis®). The drug administration apparatus was a 3cc (3 ml) needleless-syringe attached to a nasal atomizer for intranasal administration. Each dose (12, 24, and 48 IU) and placebo was administered at a total volume of 1.5 ml intranasal (≈0.75 ml per nostril). Participants were administered the nasal-spray fluid of either OT or placebo dose at a volume of 0.75ml per nostril (1.5ml total) under the supervision of a research assistant. All administrations were completed

within 8min. One spray is 4 IU and each 4 IU spray is equivalent to 0.1 ml. Thus, 12, 24, and 48 IU of OT is equal to 0.3, 0.6, and 1.2 ml of nasal spray fluid. For drug preparation, OT doses were brought to their corresponding volume (ml) in a 3cc needleless-syringe, and then each syringe was brought to a full volume of 1.5 cc by adding saline. This approach was used to blind participants to dose contents. The placebo dose contained only saline, and was also administered at a total volume of 1.5 ml (0.75 ml per nostril). Table 1.B outlines intranasal dose levels.

Dose	Volume (ml) of OT.	Corresponding volume (ml) of placebo
Placebo	0 ml	1.5 ml
OT (12 IU)	0.3 ml	1.2 ml
OT (24 IU)	0.6 ml	0.9 ml
OT (48 IU)	1.2 ml	0.3 ml

Table 1.B Outline of dose levels. Presented are the dose levels that were used for intranasal administration in Experiment 1. Dose levels varied in the concentration of OT. All Participants inhaled a total volume of 1.5ml of spray. IU = international unit.

Psychometric measures:

The Buss-Perry Aggression Questionnaire: (BPAQ; Buss, & Perry, 1992) is a self-report measure of trait aggression consisting of 29-items. It is well validated in populations with both Axis I and Axis II disorders.

The Barratt Impulsivity Scale: (BIS-11; Patton et al., 1995) is a self-report measure of the personality trait of impulsivity consisting of 30-items.

The Self-Report Psychopathy Scale III :(SRP-III; Paulhus et al., 2010; Mahmut et al., 2011). The SRP-III is a self-report measure of the clinical construct of psychopathy consisting of 64-items developed from the well-established Psychopathy Checklist-Revised (Hare & Neumann, 2008).

Impulsive Premeditative Aggression Scale: (IPAS; Stanford et al., 2003). The IPAS is a self-report measure of trait aggression, validated in prison populations, consisting of 30-items measuring aggressive acts within the last 6 months (Stanford et al., 2003).

The BPAQ, BIS-11, SRP-III, and IPAS were given a day prior to PSAP testing after consent was obtained.

The Profile of Mood States: Short Form (POMs: Shacham, 1983) is a self-report measure of psychological distress consisting of 38-adjective items on a 0-4 Likert-rating scale ranging from “Not at all” to “Extremely”. The POMS provides a total mood disturbance score and six subscale scores measuring six distinct mood states: Depression-Dejection, Anger-Hostility, Tension-Anxiety, Fatigue, Vigor, and Confusion-Bewilderment. The POMS was given 30 min

prior to dose (OT and placebo) and prior to each PSAP session following dose (OT and placebo). POMS data for each subscale were transformed into a difference score (Δ score) of Post-Dose minus Pre-Dose, to assess changes in mood following OT dosing.

Cardiovascular measures

Previous studies have noted that OT administration increases heart rate (HR) variability, an index of parasympathetic activity (Kemp et al., 2012). In both human and rodent species, OT dose has been reported to decrease blood pressure (BP) (Petersson et al., 1996; Rosseland et al., 2013). HR and BP were measured using a sphygmomanometer (BpTru Vital Signs Monitor, Coquitlam, Canada) after each session of the PSAP. Cardiovascular data (HR/BP) were collected to provide physiological confirmation of an active dose. All cardiovascular data were taken given 30 min prior to dose (OT and placebo) and 6 min after each PSAP session following dose (OT and placebo). All cardiovascular data were transformed into a difference score (Δ score) of Post-Dose minus Pre-Dose.

Outline of study days		
Study Day	**Description**	**OT Dose**
1	Baseline for PSAP	
2	PSAP with either OT or PLC	12, 24, or 48 IU of OT
3	PSAP with either OT or PLC	12, 24, or 48 IU of OT
4	PSAP with either OT or PLC	12, 24, or 48 IU of OT
5	PSAP with either OT or PLC	12, 24, or 48 IU of OT

Daily Schedule (Dose Days)		
Time point	**Session**	**Event**
8:30 am	Dose Administration	OT or PLC, POMS, HR/BP
30 min after dose 9:00 am	Post-Dose Session 1	POMS, PSAP, HR/BP
90 min after dose 10:00 am	Post-Dose Session 2	POMS, PSAP, HR/BP
150 min after dose 11:00 am	Post-Dose Session 3	POMS, PSAP, HR/BP
210 min after dose 12:00 pm	Post-Dose Session 4	POMS, PSAP, HR/BP

Table 1.C Outline of study days.
OT = oxytocin. PLC = placebo. POMS = Profile of Mood Scale. PSAP = Point subtraction aggression paradigm. HR= heart rate. BP = blood pressure. IU = international unit.

Statistical Analyses across all doses and sessions

All statistical tests were conducted using the statistical program STATA version 11.1. To test for main effects of dose and session, and the interaction of dose by session, two-way repeated measures Analysis of Variance (RM ANOVA), with two within-subjects factors (dose and session), were conducted on the following variables: the overall aggressive response rates (reponses per minute; from all doses and sessions), Δ scores from all cardiovascular data, and Δ scores from each subscale of the POMS.

Behavioral, cardiovascular, and mood data were dependent variables in the RM ANOVA. Dose and session were the independent variables in the RM ANOVA. To correct for violations against sphericity that could be associated with RM, p-values were corrected using Huynh-Feldt epsilon correction. All p-values from all RM ANOVAs are reported with both the uncorrected and Huynh-Feldt corrected p-values from the RM ANOVA model. Only the corrected p-values ($p_{Huyn\text{-}Feldtcorr}$) were used to signify statistical significance.

Behavioral data analyses at the pharmacological peak effect

Following the two-way RM ANOVA on the overall aggressive response rate across all doses and sessions, analysis of behavioral data focused on session 2, 90 min after dosing because the accumulation of neuropeptides in the cerebrospinal fluid (CSF) can be seen 30 min after intranasal administration, and levels continue to rise up to 80 min and remain stable 90-120 min after administration (Born et al., 2002). Therefore, the pharmacological peak effect was expected at approximately 90 min. The pharmacological peak effect was chosen because across all six subjects there were no observed trends by dose or by session of OT on aggressive behavior. To analyze behavioral data at the pharmacological peak effect, the overall aggressive response rate (aggressive responses per minute), the distribution of inter-response times (IRT) of aggressive responding, and the overall monetary response rate on the A button (monetary responses per second) were used as dependent variables. These two response options (A and B) are measured in different response rate units, because monetary (Button A) responding occurs more frequently than aggressive (Button B) responding during PSAP sessions (Cherek et al., 2006; Lane & Cherek, 2000).

This experiment was the first study to analyze IRT distributions of aggressive responding from the PSAP. This was an exploratory analysis of aggressive responding. The rationale for examining the distribution of IRTs during bouts of aggressive responding at the peak effect was because interim

graphical analysis of the overall aggressive response rates revealed unique patterns of change in aggressive responding under OT. It was then hypothesized that inspection of IRT distributions on a single-subject level might reveal orderly changes in aggressive responding under OT across participants that the overall aggressive response rate may have not detected (Iversen, 1991; Payla, 1992). Only the IRTs on the aggressive response option (Button B) were analyzed, as there were no trends in Button A (monetary) responding across doses, and these data were not related to the primary study hypothesis.

The overall aggressive response rate and IRT distribution of aggressive responding were both analyzed because they represent two potentially unique response dimensions. The overall aggressive response rate and IRT distributions (also known as the local response rate) of aggressive responding vary independently. In IRT distributional analysis, an increase in the interval between aggressive responses (i.e. rightward shift in IRT distribution) would demonstrate a decrease in the rate of responding within a bout of aggressive responding (FR 10). By extension, this could suggest that the social salience of provocation from the “other person” was altered. To analyze IRT data, the difference in time between consecutive responses emitted during a bout of aggressive responding (FR 10) was calculated. For each individual participant, the cumulative frequency distributions of IRTs on the aggressive response option were analyzed in order to examine the shifts in IRT distributions as a function of OT dose. Inspection of IRT distributions on a

single-subject level, such as this experiment, provides an additional level of behavioral analysis to infer changes in behavior at the millisecond timescale.

All behavioral data from session 2 (90 min post-dose; the pharmacological peak effect) were analyzed at three levels of analysis. First, statistical tests were conducted on overall response rate of aggressive responding. The second level of analysis was visual inspection of individual subject data at the session containing the pharmacological peak effect. The third level of analysis was statistical testing of participant's IRT distributions at the pharmacological peak effect, comparing all there dose levels of OT to placebo

Results

Overall aggressive response rate data across all doses and sessions

A two-way RM ANOVA on the overall aggressive response rate found no statistically significant main effects of dose ($F(3, 15) = 0.05$, $p = 0.98$, $p_{Huyn\text{-}Feldtcorr} = 0.98$) or session ($F(3, 14) = 1.2$, $p = 0.34$, $p_{Huyn\text{-}Feldtcorr} = 0.35$). There was a significant interaction of dose by session, but not after Huyn-Feldt epsilon correction for repeated measures ($F(3, 42) = 2.34$, $p = 0.03$, $p_{Huyn\text{-}Feldtcorr} = 0.15$). Data from the overall aggressive response rate for all dose levels averaged across all PSAP sessions are presented in Figure 1.A.

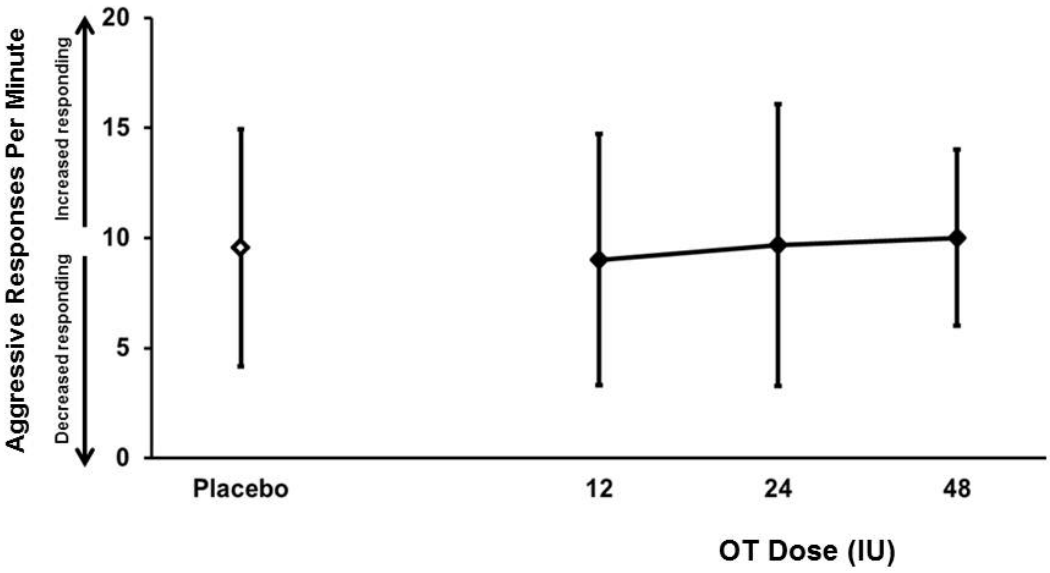


Figure 1.A Average overall aggressive response rate across dose levels. Presented are mean (S.D.) data of the overall aggressive response rate for all six subjects, across all four sessions, and all four dose levels. IU = international unit.

Pharmacological peak effect data

In the first-level of analysis, statistical tests were conducted on both aggressive and monetary behavior at 90 min post dose (session 2). The assumptions of normality and homogeneity of variance were tested for both the overall aggressive responses rate and the overall monetary responses rate. For the overall aggressive responses rate, Shapiro-Wilk's test of normality (S-W = 0.928, df (22), p = 0.07) and Levene's test of homogeneity of variance (F (3, 20) = 0.11, p = 0.84) were not significant. For monetary responses rate, Shaprio-Wilk's test of normality (S-W = 0.93 df (22), p = 0.11) and Levene's test of homogeneity of variance (3, 20) = 2.14, p = 0.18) were not significant. A one-way RM ANOVA on the overall aggressive responses rate across dose levels at session 2 (90 min post dose) was not statistically significant (F (3, 20) = 0.56, p = 0.4). A one-way ANOVA on the overall monetary responses rate across all dose levels session 2 (at 90 min post dose) was not found to be statistically significant (F (3, 20) = 1.26, p = 0.3). Descriptive summary of the aggressive responding at the session containing the pharmacological peak effect (90 min post-dose; session 2) is found in the appendix material.

The second level of analysis focused on graphical inspection of each individual participant's behavioral data (aggressive and monetary responding) at 90 min post dose. Overall aggressive response rates at 90 min post dose for each individual subject are presented in Figure 1.B. Three participants (s13121, s13234, and s13285) showed decreases in overall aggressive response rate at the 12IU OT dose compared to placebo. All other participants showed no changes in the overall aggressive response rate at the 12IU OT dose. At the 24IU dose, one participant (s13214) showed a decrease in the overall aggressive response rate. Three participants (s13121, s13146, and s13234) showed increases in the overall aggressive response rate, and two participants (s13246 and s13285) showed no changes in the overall aggressive response rate. Finally, at the 48IU OT dose two participants (s13214 and s13285) showed decreases in the overall aggressive response rates, three participants (s13121, s13146, and s13234) showed increases in the overall aggressive response rates, and one participant (s13246) showed no change in the overall aggressive response rate. As shown in Figure 1.C, no changes in the overall monetary response rate were observed across doses for any participants. The absence of change in monetarily reinforced responding provides evidence that changes in aggressive responding at 90 min post OT dose were specific to the aggressive response option and are not a stimulatory or sedative effect of OT on motor coordination.

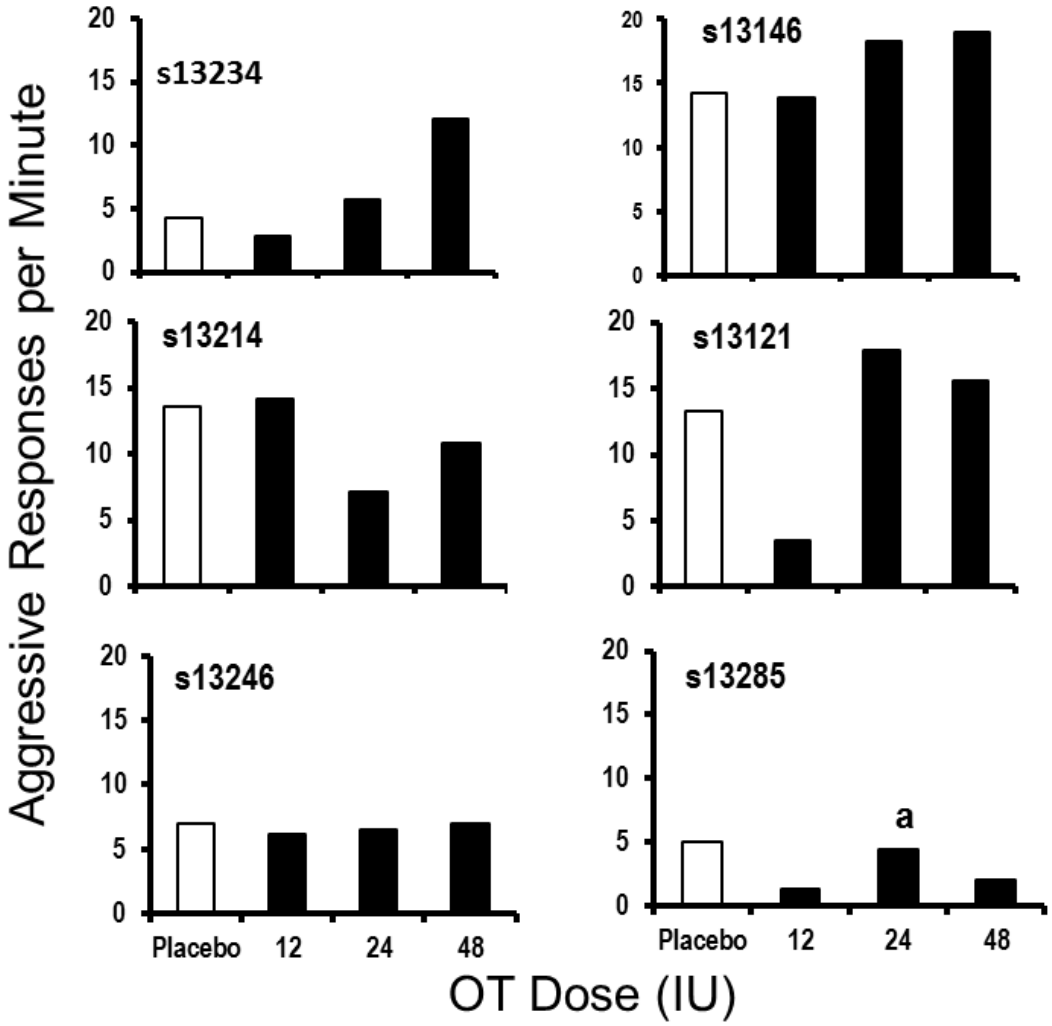


Figure 1.B Overall aggressive response rates across placebo and all three doses of oxytocin for each participant.
Aggressive response rate (responses per minute) during session 2 (90 min post dose) on the aggressive response option (y-axis) across placebo and three doses of oxytocin (x-axis).
a= Session 2 data are at 15 min instead of 25 min, due to experimenter error. IU = international unit.
Taken from Alcorn III et al. (In Press).

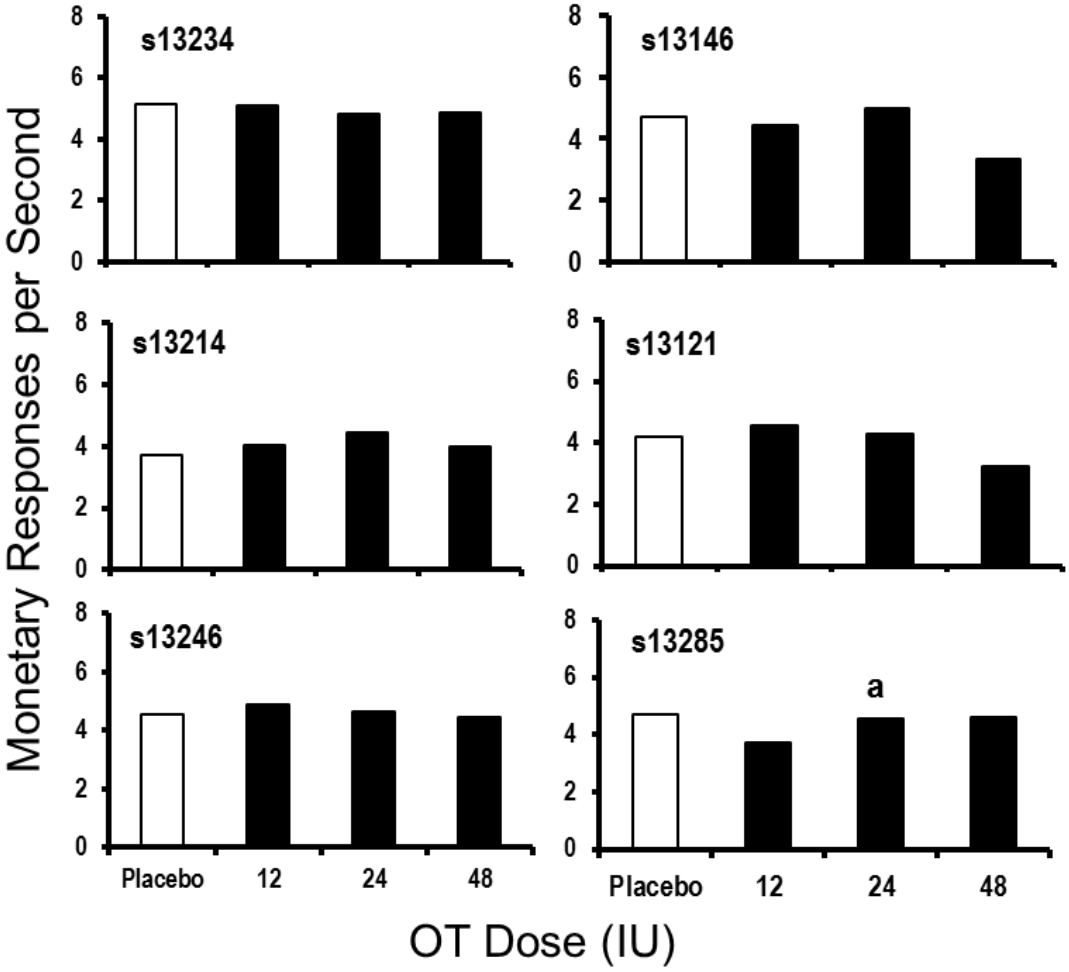


Figure 1.C Overall monetary response rates across placebo and all three doses of oxytocin for each participant.
Monetary response rate (responses per second) during session 2 (90 min post dose) on the monetary-earnng response option (y-axis) across placebo and three doses of oxytocin (x-axis).
a= Session 2 data is 15 min instead of 25 min, due to experimenter error. IU = international unit.
Taken from Alcorn III et al. (In Press).

The third level of analysis employed statistical and graphical comparisons of the IRT distributions on the aggressive option. Kolmogorov-Smirnov (K-S) tests were conducted to compare IRT distributions under each OT dose and placebo. K-S tests were chosen because IRT distributions were not normally distributed, thus the K-S tests were used because they make no assumptions regarding underlying distributions (Corder & Foreman, 2009). To correct for multiple comparisons, the Benjamini–Yekutieli false discovery rate was employed (Benjamini & Yekutieli, 2001). The Benjamini–Yekutieli false discovery rate determined that a critical p-value ($p < 0.01$) should be used to signify statistical significance. Figure 1.D shows cumulative frequency distributions of IRTs on the aggressive response option (Button B) for each subject at each dose. Twelve of the seventeen K-S tests of the IRT distributions under active OT doses were significantly different from placebo. For s13121, the distribution of aggressive IRTs was found to be significantly different from placebo only at the 24IU OT dose ($D = 0.18$, $p < 0.01$). For s13146, the distribution of aggressive IRTs was found to be significantly different from placebo at the 12IU ($D = 0.43$, $p < 0.01$) OT dose. For s13214, the distributions of aggressive option IRTs were found to be significantly different from placebo under all OT doses: 12IU ($D = 0.54$, $p < 0.01$), 24IU ($D = 0.35$, $p < 0.01$), and 48IU ($D = 0.49$, $p < 0.01$). For s13234, the distributions of aggressive IRTs were found to be significantly different from placebo under 24IU ($D = 0.36$, $p < 0.01$) and 48IU ($D = 0.413$, $p < 0.01$) OT doses. For s13246, the distributions of aggressive IRTs were found to be significantly different from placebo under the

12IU ($D = 0.218$, $p < 0.01$) and 24IU ($D = 0.58$, $p < 0.01$) OT dose. For s13285, the distributions of aggressive IRTs were found to be significantly different from placebo under the 12IU ($D = 0.99$, $p < 0.01$) and 24IU ($D = 0.33$, $p < 0.01$). Measures of central-tendency for the distribution of IRTs on the aggressive option are presented in Figure 1.E as box and whisker plots.

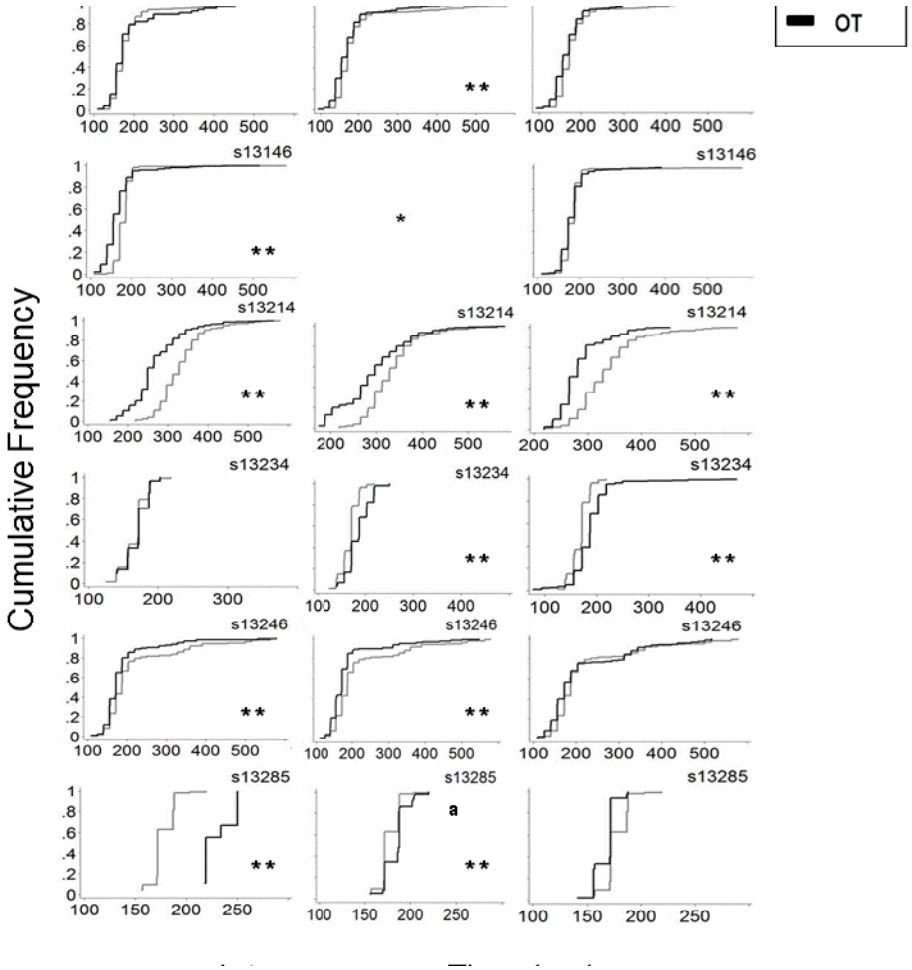


Figure 1.D Inter-response times across placebo and all three doses of oxytocin for each participant.
Data are shown as cumulative frequency distributions of IRT data on the aggressive response option across all doses from all participants. Note: different scaling on the x- and y-axes for each individual participant. * = data lost due to experimenter error. a = session lasted 15min instead of 25min, due to experimenter error. ** = p< 0.01, statistically significant from placebo, after false discovery rate correction. An increase in IRT value is indicative of decreased rate of responding during a bout of aggressive responding, whereas a decrease in IRT value is indicative of increased rate of responding during a bout of aggressive responding. IU = international unit. ms = millisecond
Taken from Alcorn III et al. (In Press)

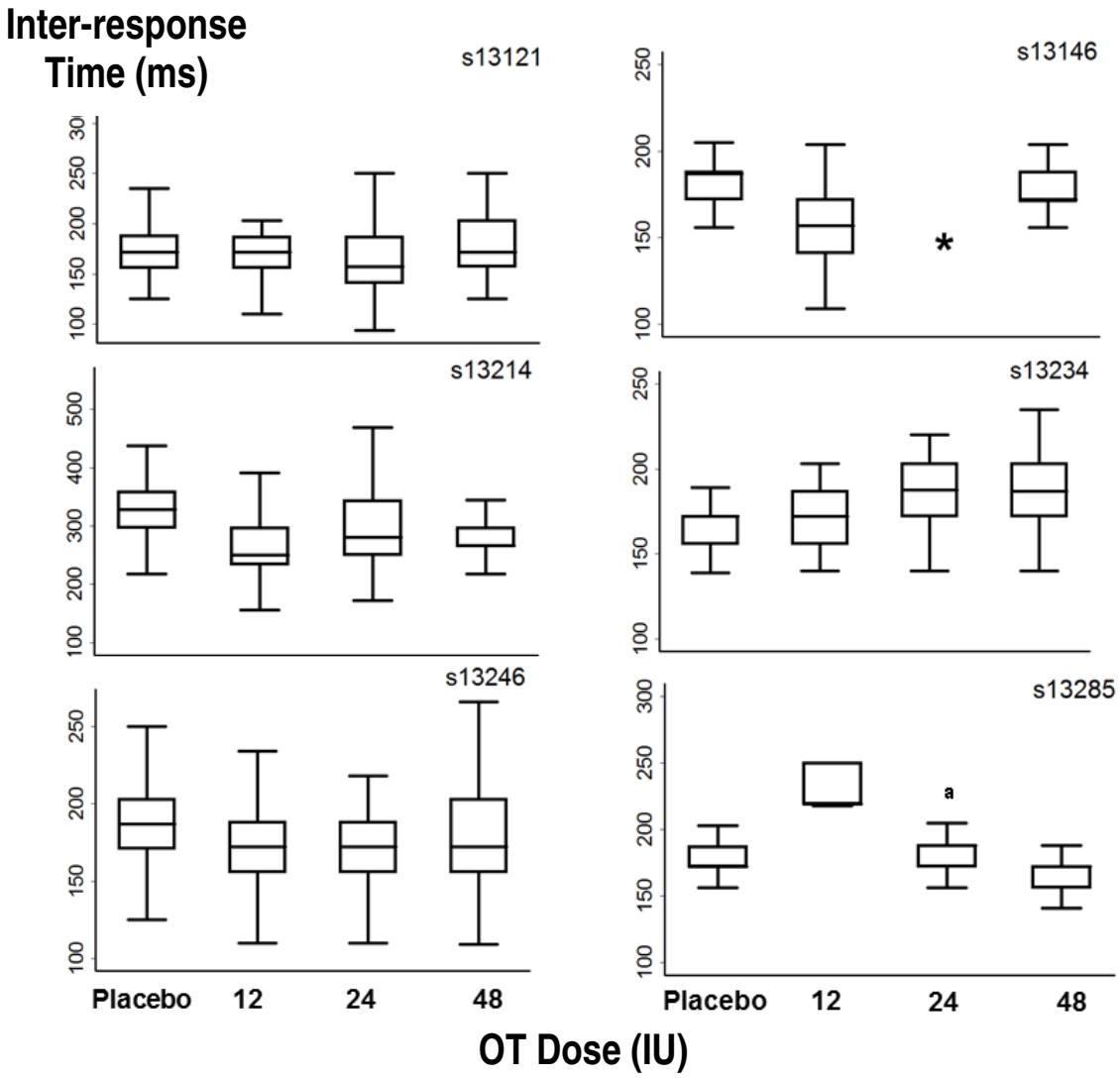


Figure 1.E Median (Inter-Quartile Range) inter-response iimes (in milliseconds) of aggressive responding across placebo and all three doses of oxytocin for each participant.
Data are presented from session 2 (90 min post dose). Note: different scales on the y-axis for each individual participant. * = data lost due to experimenter error. a = session lasted 15 min instead of 25 min, due to experimenter error. IU = international unit. ms = millisecond
Taken from Alcorn III et al. (In press).

To summarize the behavioral data (overall response rate and IRT distribution) for each participant at the pharmacological peak effect, in two participants (s13121 and s13146), a decrease and no change in the overall aggressive response rates were seen under the 12IU OT dose, respectively. Conversely, for s13121 and s13146, increases in overall aggressive response rates were seen under the 24IU and 48IU OT doses. The IRT distributions under OT were only significantly different from placebo at the 24IU and 12IU dose for s13121 and s13146, respectively; the IRT distributions for both of these participants at the respective dose levels were both shifted leftwards indicating increased local response rates. In two participants (s13214 and s13285), decreases in overall aggressive response rates were observed following OT dosing compared to placebo. For s13214, decreases in overall aggressive responses rate were observed under the 24 and 48IU OT doses. In s13214 IRT distributions under all three dose levels were significantly different from placebo and under all three doses IRT distributions were shifted leftward. For s13285, decreases in overall aggressive response rate were observed under the 12IU and 48IU OT doses, but not under the 24IU dose. In the same participant, IRT distributions were significantly different than placebo under the 12IU and 24IU OT doses; under these doses IRT distributions were shifted leftward. For participant s13234, an increase in the overall aggressive response rate was seen under the 24IU and 48IU OT doses. In the same participant, this increase in overall response rate was accompanied by significant rightward shifts in IRT distributions under the same dose levels. For participant s13246,

we observed no change in overall aggressive response rate between OT doses and placebo. However, for s13246, IRT distributions were significantly different from placebo under the 12IU and 24IU OT doses; under both dose levels the IRT distributions were shifted leftward. In conclusion, while there were observed several differences from placebo in overall aggressive response rates and IRT distributions following OT dosing, there were no systematic or orderly dose-response relationships overall. Thus, OT appeared to exert effects specifically on operationally-defined aggressive responding (rate changes were not observed for monetary-reinforced responding). However, these effects were marked by substantial individual differences.

Cardiovascular data across all doses and sessions

All cardiovascular data (Δ scores) were tested using three different two-way RM ANOVAs all testing for main effects of dose and session, and interaction of dose by session. After Huyn-Feldt epsilon correction, no RM ANOVA on any cardiovascular measure found any statistically significant main effects of dose or session, or any interaction of dose by session. Descriptive statistics of all cardiovascular data (Δ scores) are presented in Tables 1.C through 1.E. Summaries of the results from all RM ANOVAs on all cardiovascular data (Δ scores) are found in Table 1.F. Descriptive statistics of all raw cardiovascular data by session and dose are in the Appendix material.

Minutes Post-Dose (Post-Dose session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
30 min (1)	-7.8 (2.8)	-8 (5.1)	-7 (2.5)	-9.5 (4.4)
90 min (2)	-11.3 (5.4)	-12.2 (5)	-9.2 (6.1)	-12.7 (9.4)
150 min (3)	-12.6 (6.3)	-13.5 (4.7)	-14 (10)	-13.5 (9)
210 min (4)	-15.6 (6.2)	-17.4 (6.2)	-12 (5.9)	-15.2 (10)

Table 1.D Descriptive statistics of heart rate (Δ scores).
Data are presented as mean (S.D.) for each dose and each session. 30min, 90min, 150min, and 210min post dose (Session 1, 2, 3, and 4, respectively). (Δ Scores: Post-Dose minus Pre-Dose). IU = international unit.

Minutes Post-Dose (Post-Dose session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
30 min (1)	3.3 (7.1)	-2.2 (10.2)	2.3 (6.6)	1 (9)
90 min (2)	-0.2 (9.1)	0.2 (13.3)	1.5 (8.6)	7.2 (20.5)
150 min (3)	0.3 (7.1)	0.3 (14.1)	2.7 (9.4)	3.7 (6.7)
210 min (4)	7.2 (9.6)	2.6 (15.9)	6.8 (8.8)	0.2 (5.8)

Table 1.E Descriptive statistics systolic blood pressure (Δ scores).
Data are presented as mean (S.D.) for each dose and each session. 30min, 90min, 150min, and 210min post dose (Session 1, 2, 3, and 4, respectively). (Δ Scores: Post-Dose minus Pre-Dose). IU = international unit.

Minutes Post-Dose (Post-Dose session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
30 min (1)	0 (7.9)	0.3 (4.6)	0 (7.2)	0.6 (3.3)
90 min (2)	1.5 (4.9)	0.2 (7.5)	4.5 (8.6)	1.8 (5.1)
150 min (3)	0.5 (5)	-0.8 (8.6)	2.3 (9.4)	0.3 (7.0)
210 min (4)	5.4 (8.3)	1.2 (12.4)	6.8 (8.8)	1.2 (6.8)

Table 1.F Descriptive statistics of diastolic blood pressure (Δ scores).
Data are presented as mean (S.D.) for each dose and each session. 30 min, 90 min, 150 min, and 210 min post dose (Session 1, 2, 3, and 4, respectively). (Δ Scores: Post-Dose minus Pre-Dose). IU = international unit.

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn\text{-}Feldtcorr)}$
Heart Rate (Δ Scores)					
	Main				
	Dose	(3, 15)	0.63	0.61	0.60
	Session	(3, 14)	5.03	0.01	0.06
	Interaction				
	Dose X Session	(9, 42)	0.58	0.81	0.8
Systolic BP (Δ Scores)					
	Main				
	Dose	(3, 15)	0.42	0.74	0.62
	Session	(3, 14)	2.24	0.13	0.13
	Interaction				
	Dose X Session	(9, 42)	1.33	0.25	0.29
Diastolic BP (Δ Scores)					
	Main				
	Dose	(3, 15)	0.65	0.6	0.6
	Session	(3, 14)	2.1	0.15	0.15
	Interaction				
	Dose X Session	(9, 42)	0.7	0.71	0.64

Table 1.G Summaries of the RM ANOVAs on all cardiovascular data (Δ scores)
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn\text{-}Feldtcorr)}$= corrected p-value for repeated measures.
(Δ Scores: Post-Dose minus Pre-Dose)

POMS Data across all doses and sessions

All POMS data (Δ scores) were analyzed using six separate two-way RM ANOVAs (one for each subscale) all testing for main effects of dose and session, and interaction of dose by session. For planned multiple comparisons of each POMS subscale (Δ scores), the Benjamini–Yekutieli false discovery rate (Benjamini & Yekutieli, 2001) was employed (to correct for multiple comparisons across the multiple subscales) in addition to the Huyn-Feldt corrected p-values. The Benjamini–Yekutieli false discovery rate determined that a critical p-value ($p < 0.004$) should be used to signify statistical significance. After correction, no RM ANOVA on any POMS subscale found a statistically significant main effect of dose or session, or any interaction of dose by session. Descriptive statistics of all POMS subscales (Δ scores) are presented in Table 1.G. Summaries of the results from all RM ANOVAs on all POMS data (Δ scores) are found in Table 1.H. Descriptive statistics of all raw POM subscales by session and dose are in the Appendix material

Subscale	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
Depression-Dejection	-0.87 (1.7)	0.22 (0.6)	-0.4 (0.6)	0.1 (0.5)
Vigor	-0.82 (3.1)	-0.7 (2.1)	-1.2 (1.9)	-0.5 (1.6)
Confusion-Bewilderment	0 (0.5)	0 (0)	0.1 (0.4)	0 (0)
Tension-Anxiety	-0.22 (1.8)	-0.4 (1.6)	-0.4 (1.3)	-0.4 (0.9)
Anger-Hostility	-0.4 (0.9)	0.1 (0.42)	0 (0)	0.2 (0.8)
Fatigue	-1 (2.5)	0.26 (2.7)	0 (2.1)	0.2 (0.8)

Table 1.H Descriptive statistics of all POMS subscales (Δ scores)
Data are presented as mean (S.D.) for all POMS subscales.
(Δ Scores: Post-Dose minus Pre-Dose)

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn\text{-}Feldtcorr)}$
Depression-Dejection (Δ Scores)					
	Main				
	Dose	(3, 15)	2.04	0.15	0.19
	Session	(3, 14)	1.24	0.33	0.32
	Interaction				
	Dose X Session	(9, 42)	1.06	0.41	0.36
Vigor (Δ Scores)					
	Main				
	Dose	(3, 15)	1.89	0.17	0.19
	Session	(3, 14)	2.94	0.07	0.08
	Interaction				
	Dose X Session	(9, 42)	1.2	0.32	0.34
Confusion-Bewilderment (Δ Scores)					
	Main				
	Dose	(3, 15)	0.4	0.77	*
	Session	(3, 14)	1.07	0.34	0.35
	Interaction				
	Dose X Session	(9, 42)	1.03	0.43	*

Table 1.I Summaries of the RM ANOVAs on all POMS data (Δ scores)
*= corrected p-values not specified by the model.
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn\text{-}Feldtcorr)}$= corrected p-value for repeated measures
(Δ Scores: Post-Dose minus Pre-Dose)

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn-Feldtcorr)}$
Tension-Anxiety (Δ Scores)					
	Main				
	Dose	(3, 15)	0.06	0.98	0.94
	Session	(3, 14)	2.45	0.11	0.15
	Interaction				
	Dose X Session	(9, 42)	2.34	0.03	0.14
Anger-Hostility (Δ Scores)					
	Main				
	Dose	(3, 15)	2.11	0.14	0.14
	Session	(3, 14)	1.03	0.41	0.54
	Interaction				
	Dose X Session	(9, 42)	0.76	0.66	0.54
Fatigue (Δ Scores)					
	Main				
	Dose	(3, 15)	0.55	0.66	0.57
	Session	(3, 14)	2.34	0.12	0.17
	Interaction				
	Dose X Session	(9, 42)	0.32	0.96	0.79

Continued from previous page

Table 1.I Summaries of the RM ANOVAs on all POMS data (Δ scores)
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn-Feldtcorr)}$= corrected p-value for repeated measures (Δ Scores: Post-Dose minus Pre-Dose)

Psychometric data

Analyses of the psychometric scores (SRP-III, BPAQ, BIS-11 and IPAS) did not reveal any notable associations with overall aggressive response rates or IRT distributions. Psychometric scores were comparable across participants. Total scores from psychometric scales are presented in the Appendix A material.

Discussion

In individuals with ASPD and past SUD, changes in aggressive response rates and IRT distributions were observed following OT dosing, but these were not systematic or dose related. Notably, the changes did appear specific to aggressive (social) behavior; OT dosing did not appear to alter monetary-reinforced (non-social) responding. This observation is consistent with the reported role of OT in modulating social behavior (Meyer-Lindenberg et al., 2011). For three participants (s13121, s13146, s13234), increases in aggressive response rate were observed at the 24IU and 48IU OT doses. However, these changes were unrelated to shifts in IRT distributions. Shifts in IRT distributions reflect changes in local response rate during response bouts on the aggressive option. While OT doses appeared to modify IRT distributions, changes were also not dose related. While most participants responded faster during aggressive bouts (typically at higher doses), rightward shifts (slower responding) were also observed.

The neuropeptide OT has been reported to increase the saliency of both positive and negative social stimuli (Gamer et al., 2010; Guastella et al., 2008; Stripens et al., 2012). This function of OT is thought to reflect promotion of prosocial behaviors (Bartz et al., 2011) and decrease in avoidance, such as response to an angry face (Evans et al., 2010). Given that aggressive responding on the PSAP is maintained by avoidance from provocation (Cherek et al., 1990) and occurs in bouts of responding, changes in the time to complete the FR 10 on the aggressive response option (e.g. IRT distribution) could reflect changes in the social saliency of provocations. Changes in IRT distributions following OT administration may cautiously be interpreted as modification in the social salience of provocation used to elicit an aggressive response. However, the lack of orderly effects implies that OT effects on aggressive behavior were also modulated by variables that were not adequately measured in the experiment (e.g., individual differences) or non-experimental sources of variability. This possibility is supported by a study from Bartz et al. (2011), in which empathic accuracy was selectively improved in less socially proficient individuals following oxytocin administration. Acute OT administration (24 IU) has been shown to interact with state anxiety level to reduce aggressive behavior of women with high state anxiety (Campbell & Hausmann, 2013). Additionally, Norman et al. (2010) found that higher levels of loneliness (diminished social support) were significantly correlated with reduced cardiac reactivity following acute OT administration. It appears that on both behavioral and biological levels, the effects of OT administration are modulated by

individual differences. Furthermore, the relationship between OT dose and neurobehavioral changes may be non-linear.

This study has several limitations. First, our sample of participants was small and homogenous. All six participants met criteria for ASPD and past SUD, had similar psychometric scores on personality assessments (see Appendix), and had criminal and drug use histories. Thus, we are limited in drawing inferences about the effects of OT on aggressive behavior to this subset of individuals. Future studies may wish to consider using larger sample of participants, including a separate group of healthy individuals to compare with a clinically relevant sample. A second limitation of the present study is that data analysis was limited mostly to qualitative rather than quantitative techniques. While both approaches have relative advantages and disadvantages, expanding the present study to a larger sample would provide increased statistical power for future studies, which would allow greater generalizability and potentially better understanding of the direction and magnitude of effects following acute intranasal OT administration. Thirdly, the experimental design did not assess aggressive responding in between OT dose days (e.g., return to non-dosing baseline conditions between doses). Thus, this experiment was not able to assess stability in aggressive responding across dosing days. Future studies may endeavor to implement designs that assess stability (or change) in social behavior across the study (i.e., an A-B-A-C-A-D design). Lastly, there was no statistically significant result on cardiovascular data (HR/BP) or self-reported mood (POMS). Therefore, outside of the differences that were

observed on aggressive responding, we do not have additional confirmation that OT was biologically or behaviorally active. Previous studies using intranasal OT dosing have observed cardiovascular changes (Kemp et al., 2012). The present lack of orderly dose-related cardiovascular effects warrants further experimentation in a non-clinical group of healthy adults.

The hypothesis of this experiment was that OT would produce dose-dependent decreases in rates of aggressive responding. This hypothesis was tested in individuals who met criteria for ASPD and past SUD, believing these individuals are a clinically relevant group and perhaps uniquely sensitive to OT effects, as previous studies have observed diminished OT function in this population (Lee et al., 2009b; Malik et al., 2012). The results imply that OT had individual effects on aggressive responding. However, the direction and magnitude of the effect are not clear, and as such the results remain inconclusive. The results are best interpreted as qualitative information for future studies seeking to study OT effects on social behavior in high-risk populations. Further work is needed to understand individual differences that plausibly moderate OT effects on aggressive responding.

It should be noted that while many studies have touted the prosocial effects of oxytocin (Bakermans-Kranenburg & van IJzendoorn, 2013), more nuanced experiments report that prosocial behaviors are not enhanced (or even decreased) in the absence of key social cues, and a broader range of behaviors may occur, e.g., competition and ratings of envy (De Dreu et al., 2012, Declerck, et al, 2010; Shamay-Tsoory et al., 2009). Acute OT administration

may actually decrease trust and cooperation in individuals with Borderline Personality Disorder (Bartz et al., 2010), a psychiatric disorder that shares much common symptomatology with ASPD+SUD. Thus, mixed or equivocal effects are not without precedent.

This experiment observed some evidence of modulation of aggressive behavior via OT administration, but the effects were not systematic and the controlling variables remain unclear. Given that (i) OT receptors are prevalent in the cortico-limbic circuitry (Gimpl & Farhenholz, 2001; Ludwig & Leng, 2006; Lee et al., 2009a); (ii) that individuals with ASPD and past SUD have disrupted functioning in this same circuitry (Siever, 2008); and (iii) that OT appears to be evolutionarily conserved in regulating mammalian social and maternal behavior, the possibility that OT has anti-aggressive properties in individuals with deficiencies in affective control and social interaction remains a viable hypothesis and target for future experimentation.

CHAPTER 3: EFFECTS OF ACUTE OXYTOCIN DOSE ON AGGRESSIVE RESPONDING IN HEALTHY MALE CONTROLS

Introduction

In Experiment 1, there was qualitative evidence of modulation of aggressive behavior following oxytocin (OT) administration in a sample of Antisocial Personality Disordered (ASPD) and Substance Use Disordered (SUD) participants. The effects of OT were not systematic across subjects. Specifically, the direction and magnitude of OT effects were not clear.

There were several limitations in the first experiment with ASPD+SUD participants that precluded definitive interpretation of OT effects on aggressive responding. The first limitation was the design. The design of Experiment 1 did not assess any changes in ongoing levels of aggressive responding that could have arisen following OT dosing (e.g., returning to baseline, or non-dose, conditions). Thus, the design in the first experiment might not have been optimal to assess the rate of responding following repeated OT administration. The second limitation is that individual differences under OT dosing were not assessed. The possibility of individual differences across ASPD+SUD participants could not be thoroughly investigated because these participants were a relativity homogenous sample in terms of substance use history, criminal charges, and personality traits (see Appendix).

OT is known to regulate affiliative behavior and social cognitions. Experiment 1 did not assess if OT changed social judgment of the "other person" in the Point Subtraction Aggression Paradigm (PSAP). Modulation of social judgment towards prosocial cognitive processing has been reported following acute OT administration (Domes et al., 2007a; Guastella et al., 2008;

Guastella et al., 2010; Kosfeld et al., 2005; Zak et al., 2007). Experiment 1 did not measure change in social cognition in the context of aggression as measured by the PSAP.

To overcome these limitations in experimental design, Experiment 2 of this dissertation changed the experimental design to reduce intra-and inter-subject subject variability within and across test days. First, aggressive responding was normalized to a baseline (pre-dose) session. Additionally, intervening non-dose baseline test days were introduced in order to obtain stable behavior patterns prior to dosing. This strategy was better able to assess baseline shifts in aggressive responding that could be a product of unintended or uncontrolled factors. Lastly, the design of Experiment 2 utilized a single dose level of OT (24 IU), the most commonly reported dose of OT in the literature (Bakermans-Kranenburg & van IJzendoorn, 2013; Shahrestani et al., 2013). These experimental changes were undertaken to measure the frequency of aggressive behavior under more stringent experimental conditions.

The rationale for Experiment 2 follows from converging evidence that the oxytonergic system modulates human prosocial behavior such as cooperation, trust, and generosity (De Dreu et al., 2010; Kosfeld et al., 2005; Rilling et al., 2012; Zak et al., 2007). These behaviors stand in contrast to antisocial behaviors such as aggression. Oxytonergic axonal projections from the hypothalamus reach the prefrontal cortices and central amygdala, which are important brain regions in mediating social behavior for both human and nonhuman animals (Carter, 2014;Gimpl & Fahrenholz, 2001; Lee et al., 2009a;

Meyer-Lindenberg et al., 2011; Young et al., 2011). The OT receptor is prevalent throughout the neurobiological circuitry underpinning social behavior (Gimpl & Fahrenholz, 2001; Lee et al., 2009a) and the OT system is evolutionarily conserved in regulating affiliative or prosocial mammalian behavior (Lee et al., 2009a; Koehbach et al., 2013; Saltzman & Maestripieri, 2011). Thus, increases in prosocial behavior should manifest as decreases in antisocial behaviors, including aggression.

Experiment 2 Hypothesis and aims.

The primary hypothesis of Experiment 2 is that acute administration of OT will decrease human aggressive behavior. Additionally, it was hypothesized that OT effects on aggression would be related to individual differences (related to psychopathy and aggression); and OT would modulate social judgment by increasing likability ratings. Accordingly, the following three aims were proposed. To test this hypothesis, three aims were proposed.

Aim 2a: To test if acute OT dose (24 IU) decreases aggressive behavior.

Rationale: To date, the majority OT studies in human participants have employed between-subjects design (Bakermans-Kranenburg & van IJzendoorn, 2013; Bethlehem, et al., 2013) and have focused on prosocial behaviors. This experiment will test if acute administration of OT decreases the frequency of aggressive responding, an antisocial behavior, in healthy male participants using a within-subjects design.

Hypothesis 2a: Compared to placebo, OT administration will reduce aggressive behavior in healthy adult male participants.

Aim 2b: To explore if personality traits of interpersonal manipulation and anger are correlated with aggressive behavior under OT.

Rationale: Psychiatric and clinically relevant personality traits such as psychopathy exist on a spectrum. All people, including those without psychiatric disorders, demonstrate some level of clinically relevant traits. Therefore, exploring the association between clinically relevant personality traits and aggressive responding under OT dosing could provide unique information regarding the manner in which OT modulates aggression as a function of individual differences in antisocial traits. The personality trait of interpersonal manipulation was selected because (i) interpersonal manipulation is a psychopathic trait and is prominent in ASPD+SUD individuals (Alcorn III et al., 2013) and (ii) individuals with higher levels of interpersonal manipulation have higher levels of aggression (Nouvion et al., 2007; Vaillancourt & Sunderani, 2011). Anger was selected as an important trait because anger reactivity and poor anger regulation are risk factors for individuals with a history of violent behavior (Alia-Klien et al., 2009), and because anger is a major affective component that accompanies aggressive behavior (Buss & Perry, 1992). Lee et al. (2009b) reported that in personality-disordered individuals, cerebrospinal fluids of OT were inversely correlated to acts of aggression. Alcorn III et al. (2013) reported that psychopathic and aggressive personality traits were two

key psychometric measures that characterized ASPD+SUD individuals from healthy volunteers. By extension, antisocial traits such as interpersonal manipulation and anger should be negatively correlated with aggression following OT dosing. This aim focuses on individual differences that could moderate OT effects.

Hypothesis 2b: Personality traits of interpersonal manipulation and anger will be negatively correlated with aggressive responding following OT dosing.

Aim 2c*:* To test if acute OT dosing (24 IU) changes social judgment following an aggressive encounter.

Rationale: Given that OT is a neuropeptide which modulates socio-emotional behaviors and cognitions, this aim tests the effect of OT dose on social judgment of the "other person" in the PSAP. To measure changes in social judgment, this aim will measure how much participants rate the likability of the "other person" in the PSAP. By measuring social judgment, this aim tests if OT dosing changes social judgment following a social interaction that elicits aggression. Given that OT in humans increased both trust behavior (Kosfeld et al., 2005) and generosity (Zak et al., 2007) towards strangers, and that affiliative social behavior towards a conspecific is known to be modulated by OT (Carter et al., 1995; Williams et al., 1994); acute OT dosing should modify participant's judgment of the "other person".

Hypothesis 3: Healthy adult male participants, OT dosing will increase prosocial ratings of likability compared to placebo.

Materials and Methods

All experimental procedures in this study were reviewed and approved by the Institutional Review Board for the University of Texas Health Science Center-Houston, USA. Prior to study participation, informed consent was obtained from all participants.

Participants:

Participants were recruited from a community sample by local newspaper advertisements. Potential subjects (18-50 years of age) were first screened though an initial phone interview to obtain information about recreational drug use, psychiatric, and medical history. Potentially eligible participants were scheduled for more extensive in-person screening. Prior to study participation all participants underwent a physical exam to screen for exclusionary medical conditions (e.g. HIV, seizures, cardiovascular, kidney or endocrine diseases, diabetes, hypertension, and history of head trauma or loss of consciousness > 20 minutes) and current use of prescription medication. These selection criteria were modeled after a recent review of safety, side-effects, and subjective reactions associated with intranasal OT administration by MacDonald et al. (2011). All potential participants had no medical history of head trauma, loss of consciousness (>20 min), hypertension, diabetes, or

cardiovascular, kidney, or endocrinological diseases/disorders (e.g. thyroid or adrenal diseases), and preservative allergies. Female participants were excluded from this experiment for the following reasons, (i) the neuropeptide oxytocin increases levels of luteinizing hormone (Evans et al., 2003) which could have potentially affect the regularly occurring menstrual cycles of female participants, and (ii) currently there are no data about interactions of oxytocin administration with oral contraceptives (i.e. birth control), introducing possible behavioral and physiological side effects. All participants were interviewed using the Structured Clinical Interview for the DSM-IV (SCID). The SCID-I is a semi-structured interview for making diagnosis of Axis I Disorders (First et al., 1996) and the SCID-II NP is a semi-structured interview for making diagnosis of Axis II Disorders (Personality Disorders; First et al., 1997). The SCID-I and SCID-II were administered by a trained mental health professional. The SCID-I and SCID-II NP was used to ensure that all potential participants did not meet DSM-IV criteria for any psychiatric disorders. Participants who qualified for study participation were provided informed consent about the study. All qualified participants were male, had no medical complications, and had no history of DSM-IV Axis I psychotic, anxiety, substance dependence, and/or mood disorders and DSM-IV Axis II personality disorder.

Extraneous drug use was monitored by daily urine samples and expired alcohol breath samples prior to beginning participation. Urine samples were screened for extraneous drugs using the Enzyme Multiple Immunoassay Technique Drug Abuse Urine Assay (Innovacon; San Diego, CA). Expired

breath samples were used for detecting alcohol consumption, prior to participation. Expired breath samples were analyzed using an Alcosensor III. Psychoactive medication was prohibited during study participation and caffeine consumption was prohibited upon entering the laboratory.

Exclusion:

Participants were excluded if they did not use the aggressive response option or if aggressive responding was below two aggressive responses per minute. This criterion was selected because the hypothesis of this experiment is that OT dose decreases aggressive behavior and cannot be examined if aggressive responding does not occur or if aggressive responding occurs at a rate close to zero (i.e., below two aggressive responses/minute; a floor effect). Additionally, if stability criteria could not be established within five consecutive days of study participation, participants were excluded. Table 2.A lists the number of participants excluded from study participation. The Shipley Institute of Living Scale-2 (Shipley et al., 2009) is a test of general cognitive aptitude consisting of a 40-item vocabulary test and a 26-item block test. The Shipley Institute-2 was used to assure that behavioral data in the PSAP were not confounded by associations with deficits in cognitive abilities. Average composite verbal and block score on the Shipley-II was 210.4 (SD = ± 21.8: age-adjusted normative percentile on the Weschler Adult Intelligence Scale estimated mean of 106.2). Thirty five participants were consented to Experiment 2, of which 17 completed the study. Reasons for exclusion from

participation are presented in Table 2.A. Demographics of participants who completed the experiment are presented in Table 2.B.

Reason for exclusion	number of participants
Aggressive responding on the PSAP did not meet criteria.	12
More than two positive detections of extraneous drug use or BAL.	1
Failure to show up for more than two consecutive study days (without prior contact).	3
Declined study participation prior to dose.	2

Table 2.A The number of participants excluded from study participation.

Demographic variable	Descriptive statistic Sample size (n = 17)
Age	
Mean (S.D.)	32 (9.2)
Years of Education	
Mean (S.D.)	13.6 (2.1)
Ethnicity	
African American (%)	53
White (%)	17.6
Hispanic (%)	29.4

Table 2.B Participant demographics.

Procedure:

Details of the Point Subtraction Aggression Paradigm (PSAP) and the apparatus in which sessions of the PSAP were conducted are identical to those listed in the materials and methods of Experiment 1. The escape response option (Button C) was not analyzed in this experiment as not all participants used the escape response and those who did use the C button often did so non-systematically. Thus, direct comparison of escape responding to both aggressive and monetarily-reinforced responding under both OT and placebo dose was not possible.

Stability criteria:

To reduce intra-subject variability this experiment included baseline (no-dose test days) in between those days in which participants were dosed. All participants had to meet stability criteria on a baseline day prior to dosing. Stability criteria was defined as (i) no ascending or descending trends in aggressive responding and (ii) participant‘s aggressive response rate (aggressive response per minute) was ≤ 0.25 on the coefficient of variation (CV: SD/mean) across all PSAP sessions on baseline days. On experimental days in which participants were scheduled to be dosed, the dose was not given unless their aggressive response rate (aggressive response per minute) during their baseline (Pre-Dose) session was within ±25% of the mean aggressive responding on the preceding baseline day. If a participant’s aggressive responding on the baseline (Pre-Dose) session was ≥ ±25% of his mean

baseline aggressive responding, neither OT nor placebo dose was introduced. Instead, an additional baseline day was run. These stability criteria were used to ensure that each participant's aggressive behavior was stable between doses and any shifts in baseline responding did not bias dosing data. These criteria were modeled after previous studies utilizing the PSAP with acute drug administration (Cherek et al., 1990; Cherek et al., 1999).

Physiological measures

Cardiovascular data were collected to provide confirmation of active OT. Heart rate (HR) and blood pressure (BP) were measured using a sphygmomanometer (BpTru Vital Signs Monitor, Coquitlam, Canada) after each session of the four PSAP sessions. Cardiovascular data (HR/BP) were collected to examine changes in autonomic nervous system activity after OT dosing, which can provide physiological confirmation of an active dose. All cardiovascular data were transformed into a difference score (Δ score) of Post-Dose minus Pre-Dose.

Body temperature (BT) was collected orally (sub-lingual) using a thermometer (Lumeon, Jacksonville, FL) four times prior each PSAP session. The decision to include BT data in this experiment was based on data in the literature showing that OT dose can decrease body temperature (Hicks et al., 2013). All BT data were transformed into a difference score (Δ score) of Post-Dose minus Pre-Dose.

Psychometric measures

The Social Visual Analog Scale (VAS) is a self-report measure of social judgment rating of the likability of other individuals. The Social VAS consisted of one question, “Right now, the person I’m paired with is” ranging from “Very likable” to “Very unlikeable”, with scores ranging from 6 – 0, respectively. All Social VAS data were collected after each of the four PSAP sessions. Social VAS ratings were transformed into a difference score (Δ score) of Post-Dose minus Pre-Dose.

The Self-Report Psychopathy Scale III (SRP-III; Paulhus et al., 2010; Mahmut et al., 2011) is a self-report measure of the clinical construct of psychopathy. The SRP-III consists of 64-items on a 1-5 point Likert-rating scale ranging from “Disagree Strongly” to “Agree Strongly”. The SPR-III provides a total score in addition to four subscale scores measuring interpersonal manipulation, callous affect, erratic lifestyle, and criminal tendencies. The subscale of interpersonal manipulation was used for correlational analysis based on Vaillancourt & Sunderani (2011).

The Buss-Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992) is a self-report measure of trait aggression consisting of 29-items on a 1-5 point Likert-rating scale ranging from “Not like me at all” to “A lot like me”. The BPAQ provides a total score in addition four subscale scores measuring physical aggression, verbal aggression, anger, and hostility. The subscale of anger was used for exploratory correlational analysis based on Alia-Klien et al. (2009).

The Profile of Mood States: Short Form (POMS; Shacham, 1983) is a self-report measure of psychological distress consisting of 38-adjective items on a 0-4 Likert-rating scale ranging from “Not at all” to “Extremely”. The POMS provides a total mood disturbance score and six subscale scores measuring six distinct mood states: Depression-Dejection, Anger-Hostility, Tension-Anxiety, Fatigue, Vigor, and Confusion-Bewilderment. These measures were used to monitor subject mood throughout the course of the experiment. All POMS data were collected before each of the four PSAP sessions. POMS data for each subscale were transformed into a difference score of Post-Dose minus Pre-Dose (Δ score), and were used to assess dose-related changes in mood.

Drug Administration:

Drug administration procedures were identical to those drug administration procedures detailed in Experiment 1. However, only one dose level (24 IU) of OT was used. Given that the three post-dose PSAP sessions of the PSAP sessions occurred over a span of more than two hours, a single dose of OT spray was hypothesized to be sufficient to observe acute effects. An outline of intranasal administration is detailed in Table 2.C.

Dose	Volume (ml) of OT.	Corresponding volume (ml) of placebo
Placebo	0 ml	1.5 ml
OT (24 IU)	0.6 ml	0.9 ml

Table 2.C Outline of dose levels.
Presented are the dose levels that were used for intranasal administration in Experiment 2. Dose levels varied in the concentration of OT. All Participants inhaled a total volume of 1.5ml of spray. IU = international unit.

Design:

Participants completed a minimum of four study days. However, this experiment contained contingencies to establish behavioral stability on aggressive responding prior to dosing. Therefore, some participants participated in the study for more than four days to achieve stability prior to and in-between doses. Participants came to the lab 2-4 days a week, from 8:00 am to approximately 12-1 pm for each study day. Participants completed four PSAP sessions on each study day (both baseline and dose days). On study days in which participants were dosed, the first session occurred 30min before dose administration and the remaining three PSAP sessions occurred at 30min, 90min, and 150min post-dose. Each PSAP session lasted 25min. Mood and temperature data were collected prior to PSAP sessions. Cardiovascular and likability ratings were collected after the PSAP sessions. An outline of experimental days is presented in Table 2.D.

Outline of study days		
Study Day	**Description**	**Comment**
1	Baseline for PSAP	May have required several days
2	PSAP with either OT dose (24 IU) or PLC	
3	Baseline for PSAP	May have required several days
4	PSAP with either OT dose (24 IU) or PLC	

Daily Schedule (Dose Days)		
Time point	**Session**	**Event**
30 min before dose 8:30 am	Baseline (Pre-Dose)	BT, POMS, PSAP, Social VAS, HR/BP
9:00 am	Dose Administration	OT (24 IU) or PLC
30 min after dose 9:30 am	Post-Dose Session 1	BT, POMS, PSAP, Social VAS, HR/BP
90 min after dose 10:30 am	Post-Dose Session 2	BT, POMS, PSAP, Social VAS, HR/BP
150 min after dose 11:30 am	Post-Dose Session 3	BT, POMS, PSAP, Social VAS, HR/BP

Table 2.D Outline of study days.
OT = oxytocin. PLC = placebo. BT = body temperature. POMS = Profile of Mood Scale PSAP = Point subtraction aggression paradigm. Social VAS = Social VAS (likability ratings). HR= heart rate. BP = blood pressure.

Data Analyses

The data analysis strategy for the behavioral data in Experiment 2 was similar to Experiment 1 (Chapter 2) and is detailed in the ensuing sections. Only the dependent variables (behavioral, physiological, social judgment, and mood) collected from the two study days in which participants were dosed were analyzed (OT, placebo).

Behavioral data

The dependent measure of aggression in the PSAP was the number of aggressive response rate (aggressive responses per minute). On days in which participants were given a dose of OT (24 IU) or placebo, aggressive response rates from each of the subsequent post-dose sessions (30 min, 90 min, 150 min post-dose represent post-dose sessions 1, 2, 3, respectively) were normalized to the baseline (pre-dose) session and were calculated as a percent of baseline = (aggressive response rate, percent of $\text{baseline}_{\text{Pre-Dose}}$: (Post-Dose Session/ Pre-Dose Session) *100). This normalized aggressive response rate was used to compare aggressive responding under OT to placebo dose.

Unlike Experiment 1 (chapter 2), the peak effect was identified behaviorally for each individual subject. Behavioral peak effect of OT was defined as the session containing the biggest change in responding from the baseline under OT (24 IU) dose. For example, if a participant's biggest change in aggressive responding under OT occurred at 90 min post-dose, then the 90 min post dose session under placebo was used. This method of defining peak

effect follows from behavioral pharmacological studies examining aggressive responding in the PSAP (Cherek & Lane, 2001), choice proportions in decision making tasks (Lane et al., 2008; Lane & Gowin, 2009), self-administration of drugs (Stoops et al., 2012), drug subjective effects (Stoops et al., 2008; Rush et al., 2011), and drug discrimination procedures (Sevak et al., 2009). All of the cited studies examined different drug effects over the course of several sessions throughout the respective experiments, but focused on peak effects. The corresponding session under placebo was used to test for differences in aggressive responding vs OT. In other words, if the peak effect for OT was observed in the session 90min post-dose, then it was compared to the session that was 90min post-dose under placebo. Across all participants, 29.4% of peak effects occurred 30 min post-dose, 23.5% of peak effects occurred 90 min post-dose, and 47.1% of peak effects occurred 150 min post-dose.

Physiological data

Cardiovascular (HR/BP) and BT data were collected to examine changes in physiological activity. Physiological data were tested to provide confirmation of biologically active OT effects, compared to placebo. All physiological data were transformed into a difference score (Δ score) of Post-Dose minus Pre-Dose.

Psychometric data

To explore the correlation between aggressive responding under OT and personality traits of interpersonal manipulation and anger (aim 2b), scores from the interpersonal manipulation subscale from the SRP-III and the anger subscale on the BPAQ were both independently standardized to have a mean of 0 and a standard deviation of 1. Standardized scores (Z-Scores) of interpersonal manipulation and anger were added together to create a composite score. Descriptive summaries of all subscales and total scores from the SRP-III and BPAQ are presented in Appendix 2.

Missing data

One participant dropped out prior to receiving the placebo dose and completing the psychometric data. To handle missing data from this participant, imputation was conducted. The sample mean of aggressive response rate (percent of $\text{baseline}_{\text{Pre-Dose}}$), Social VAS, and all physiological data for each post-dose session under placebo was imputed for this subject to provide non-biased but balanced cells for statistical analysis. Psychometric scores were also imputed using the sample mean all psychometric measures.

Statistical Analyses

All statistical tests were conducted using the statistical program STATA version 11.1. A two-way Repeated Measures Analysis of Variance (RM ANOVA) tested for main effects of dose and session, and the interaction of dose by session. The two within-subjects factors were dose (Placebo vs OT) and session (30, 90, and 150 min post-dose). The following variables were analyzed: aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$), Δ scores from the Social VAS data, Δ scores from all cardiovascular data, Δ scores from all BT data, and Δ scores from each subscale of the POMS. Behavioral, Social VAS, cardiovascular, BT, and mood data were dependent variables in the RM ANOVA. Dose and session were coded in the RM ANOVA model as factors. To correct for violations against sphericity that could be associated with RM, p-values were corrected using Huynh-Feldt epsilon correction. All p-values from all RM ANOVA are reported with both the uncorrected and Huynh-Feldt corrected p-values ($p_{Huyn\text{-}Feldtcorr}$) from the RM ANOVA. Only the Huyn-Feldt corrected p-values were used to evaluate statistical significance.

Since behavioral peak effect data were individually selected for each participant and behavioral peak effects did not occur at the same time point across participants, peak effect data were analyzed separately. For behavioral peak effect data, a paired samples t-test was to compare aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$), under OT dose to placebo. Assumptions of normality and homogeneity of variance were evaluated using the Shapiro-Wilk test and Levene's test, respectively. If violations in normality and/or

homogeneity of variance occurred, a Wilcoxon Signed-Rank Test was conducted, the nonparametric version of a paired-samples t-test.

Correlational analysis for aim 2b was conducted using Pearson's correlation coefficient. Given that there were six POMS subscales were collected and Δ scores were collected at three time points across two dose levels, the Benjamini–Yekutieli false discovery rate was employed (Benjamini & Yekutieli, 2001) to correct for multiple comparisons. The Benjamini–Yekutieli false discovery rate determined that the corrected critical p-value for all POMS data was $p < 0.003$.

Grubbs test for outliers (Grubbs, 1969) was conducted on all dependent variable prior to the two-way RM ANOVA. Grubbs test revealed outliers in aggressive response rate (percent of $\text{baseline}_{\text{Pre-Dose}}$), Social VAS (Δ scores), HR, Diastolic BP, and the Tension-Anxiety subscale of the POMS. For these variables, analyses were conducted with and without the outliers.

Results

Behavioral Data

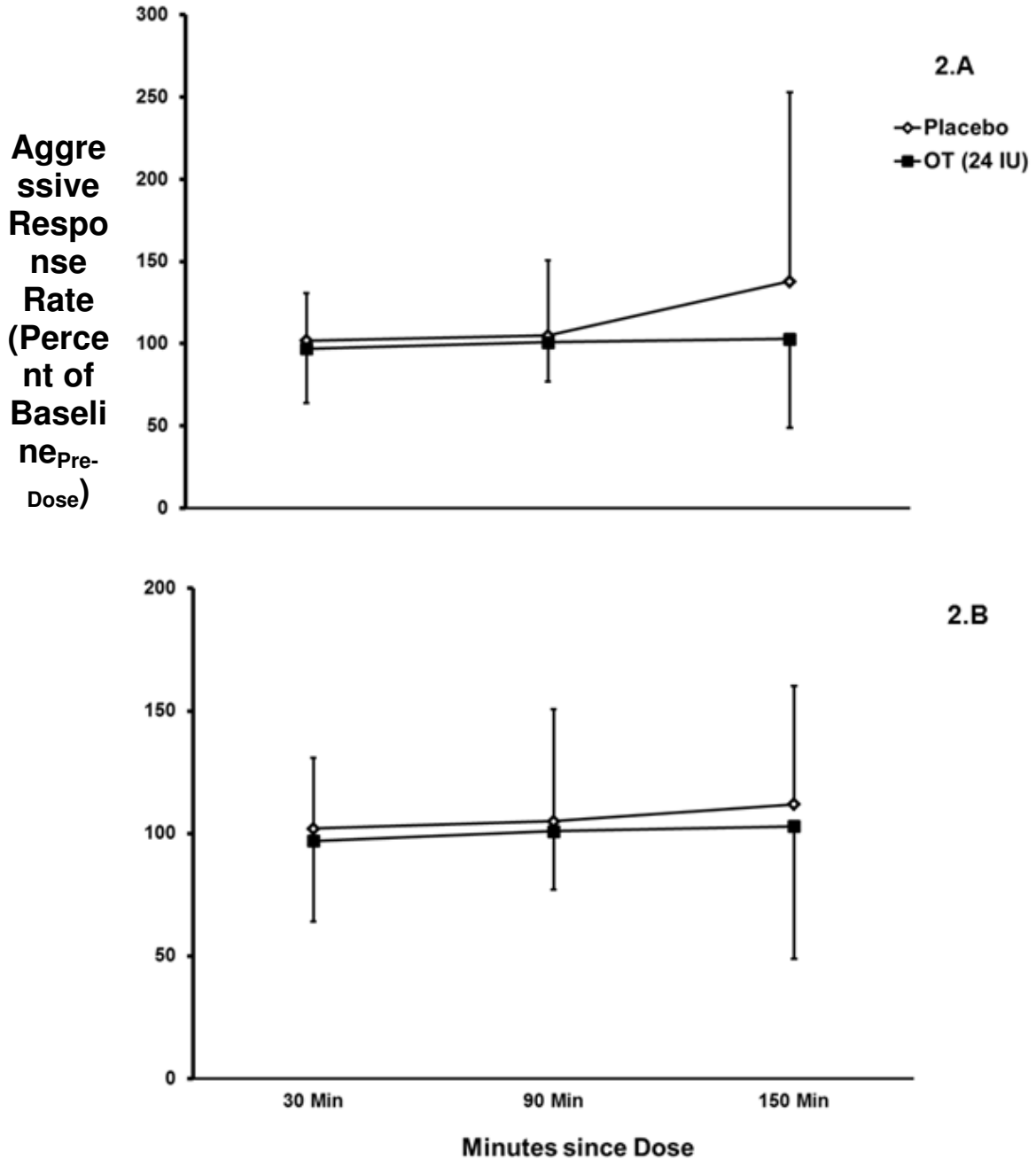
All aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$) were tested using a two-way RM ANOVA testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and interaction of dose by session. The RM ANOVA found no statistically significant main effect of dose or session. There was no statistically significant interaction of dose by session. The results of the RM ANOVA without the outlier found no statistically significant main effect of dose or session, or any interaction of dose by session. Descriptive statistics for aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$) are presented in Table 2.E. Summary results from the RM ANOVAs are presented in Table 2.G. Visual presentation of aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$) with and without the outlier are presented in Figures 2.A through 2.D, for both the OT and placebo dose.

Aggressive Response Rate	Minutes since Dose (Post-Dose Session)	Mean (S.D.)
Placebo n = 17		
	30 min	102 (28)
	90 min	105 (45)
	150 min	138 (115)[1] 112 (48.3)[2]
OT (24 IU) n = 17		
	30 min	97 (34)
	90 min	101 (24)
	150 min	103 (54)

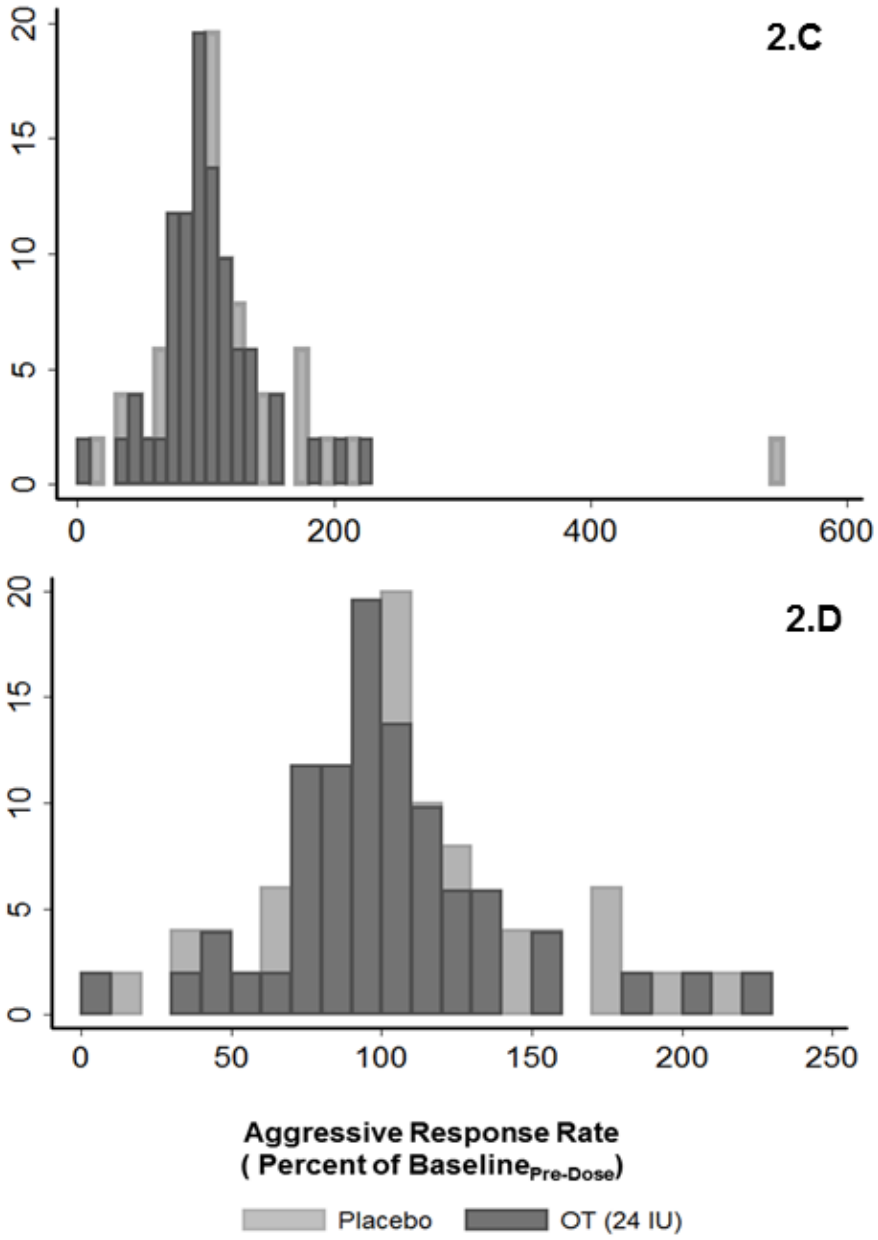
Table 2.E Descriptive statistics of aggressive responding (percent of baseline$_{\text{Pre-Dose}}$) across all post-dose sessions for both doses. Presented are mean (S.D.) of the aggressive response rate data (percent of baseline$_{\text{Pre-Dose}}$). Superscript 1 refers to data with the outlier. Superscript 2 refers to data without the outlier. IU = international unit. n = sample size.

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn-Feldtcorr)}$
Aggressive Response Rate[1]					
	Main				
	Dose	(1, 16)	0.78	0.39	0.39
	Session	(2, 32)	1.51	0.23	0.24
	Interaction				
	Dose X Session	(2, 32)	1.65	0.21	0.22
Aggressive Response Rate[2]					
	Main				
	Dose	(1,16)	0.63	0.48	0.48
	Session	(2, 32)	1.05	0.36	0.36
	Interaction				
	Dose X Session	(2, 31)	0.6	0.56	0.56

Table 2.G Summaries of the RM ANOVAs on aggressive response rates (percent of $baseline_{Pre-Dose}$).
Aggressive Response Rate[1] refers to RM ANOVA model with the outlier in the aggressive response rate data (percent of $baseline_{Pre-Dose}$).
Aggressive Response Rate[2] refers to RM ANOVA model without the outlier in the aggressive response rate data (percent of $baseline_{Pre-Dose}$).
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn-Feldtcorr)}$= corrected p-value for repeated measures



Figures 2.A and 2.B aggressive response rates (percent of baseline$_{Pre\text{-}Dose}$) across three post-dose sessions for both doses.
Presented are mean (S.D.) of the aggressive response rates (percent of baseline$_{Pre\text{-}Dose}$) over the course of three post-dose time-points (sessions) for both dose levels. Minutes since dose: 30 Min, 90 Min, and 150 Min represent Post-Dose Session 1, 2, and 3, respectively. Figure 2.A contains data with the outlier. Figure 2.B contains data without the outlier. IU = international unit.



Figures 2.C and 2.D Histograms of aggressive response rates (percent of baseline$_{Pre\text{-}Dose}$).
Presented are the distributions of aggressive response rates (percent of baseline$_{Pre\text{-}Dose}$; x-axis) for both dose levels. The y-axis represents the percent of data observations within a bin (units of 10). Figure 2.C contains data with the outlier. Figure 2.D contains data without the outlier.
IU = international unit.

Behavioral peak effect data

Peak effect data of aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$) under OT (mean = 101.8, S.D. = 58.5) and placebo (mean = 110.4, S.D. = 44.3) were tested for violations of statistical assumptions. Shapiro-Wilk test of normality (S-W = 0.99, df (32), p = 0.99) was not significant and the Levene's test of homogeneity of variance (F (1, 32) = 0.67, p = 0.41) was not significant. A paired-samples t-test comparing aggressive response rate (percent of $baseline_{Pre\text{-}Dose}$) at the peak effect data under OT to placebo dose for aggressive responding was not significant, t (16) = (-0.44, p = 0.65). Figure 2.E shows a dot plot of individual participant data for aggressive response rate (percent of $baseline_{Pre\text{-}Dose}$), at the peak effect data under OT and placebo dose.

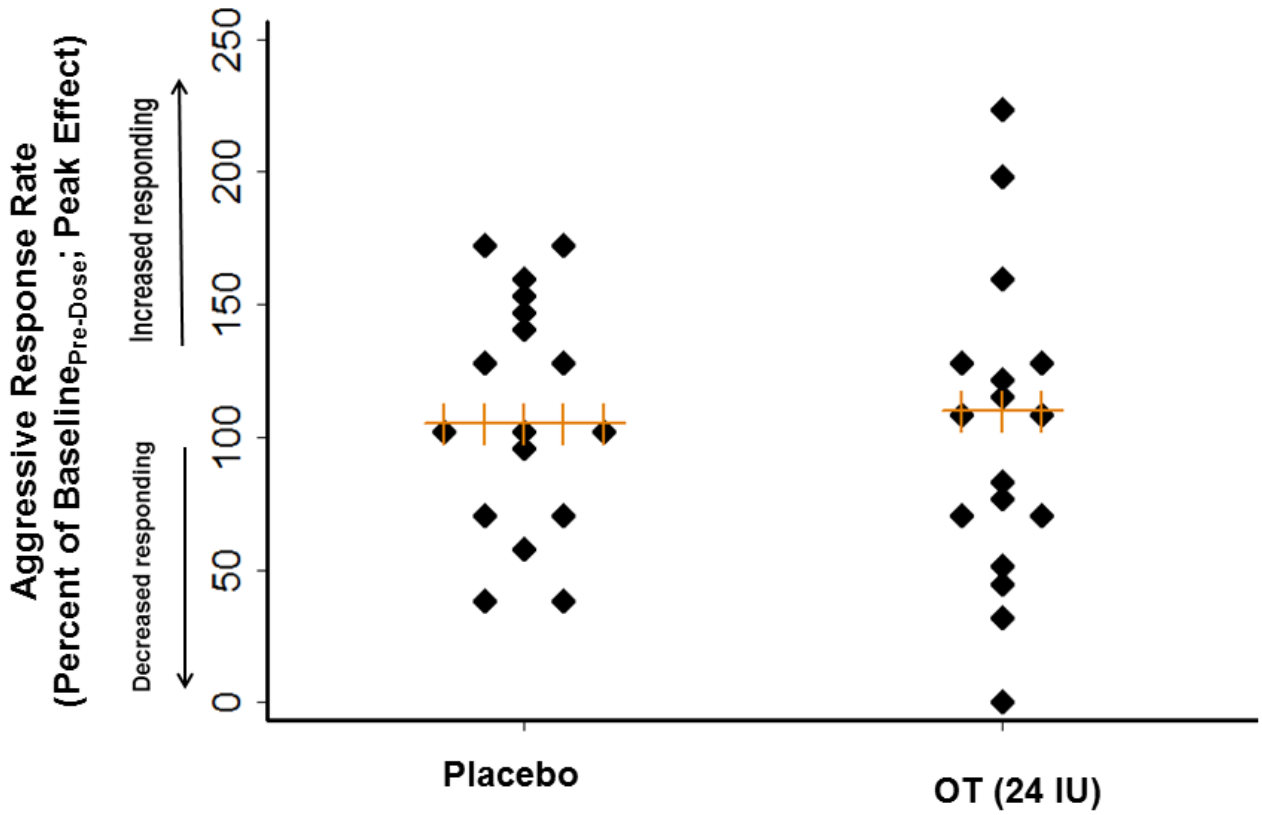


Figure 2.E Distributions of aggressive response rates (percent of baseline$_{Pre-Dose}$) at the behavioral peak effect. Presented are the distributions of aggressive response rates at the peak effect for both dose levels. Black diamonds represent individual data points for each participant. Orange crosses represent the median value of aggressive response rates (percent of baseline$_{Pre-Dose}$). OT median = 110 (IQR: 72 – 130). Placebo median = 105 (IQR: 70 - 149). IU = international unit.

Behavioral data and personality traits.

The Pearson r correlation coefficient between average aggressive response rates (percent of $baseline_{Pre\text{-}Dose}$) under OT and standardized scores of interpersonal manipulation + anger was statistically significant ($r(16) = 0.57$, $p = 0.01$). This result is opposite to the hypothesis of aim 2b. A scatter plot of average aggressive response rate under OT and combined interpersonal manipulation + anger scores is presented in Figure 2.F. Correlation coefficients between average aggressive response rate (percent of $baseline_{Pre\text{-}Dose}$) under placebo and standardized scores of combined interpersonal manipulation + anger were not statistically significant with the outlier (spearman $rho(16) = -0.03$, $p = 0.9$) or without ($r(16) = -0.15$, $p = 0.54$).

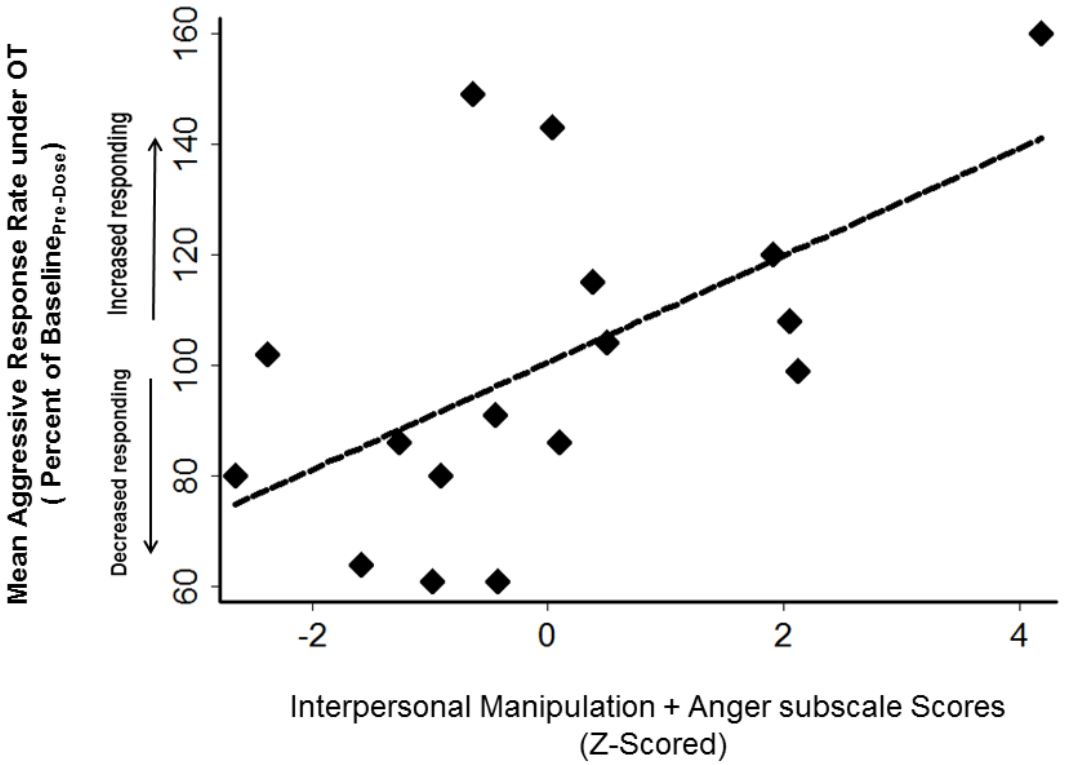


Figure 2.F Scatterplot of aggressive response rates (percent of baseline$_{Pre\text{-}Dose}$) under OT dose and combined psychometric scores of Interpersonal Manipulation and Anger.
Plotted are mean aggressive response rates under OT on the y-axis and combined subscales scores of Interpersonal Manipulation and Anger (Z-Scored) on the x-axis. Mean refers to the mean of all three post-dose sessions with aggressive responding from each post-dose session converted as a percent of the Baseline$_{Pre\text{-}Dose}$ session.

Social VAS data

All Social VAS ratings of "likability" (Δ scores) were tested using a two-way RM ANOVA testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and interaction of dose by session. The RM ANOVA found no statistically significant main effect of dose or session. There was no statistically significant interaction of dose by session. The results of the RM ANOVA without the outlier found no statistically significant main effect of dose or session, or any interaction of dose by session. Figures 2.G and 2.H show Social VAS ratings of "likability" for both OT and Placebo across all post-dose sessions. Descriptive statistics for all sessions across both dose levels are found in Table 2.H. Summary results from RM ANOVAs on Social VAS ratings of "likability" (Δ scores) are found in Table 2.I.

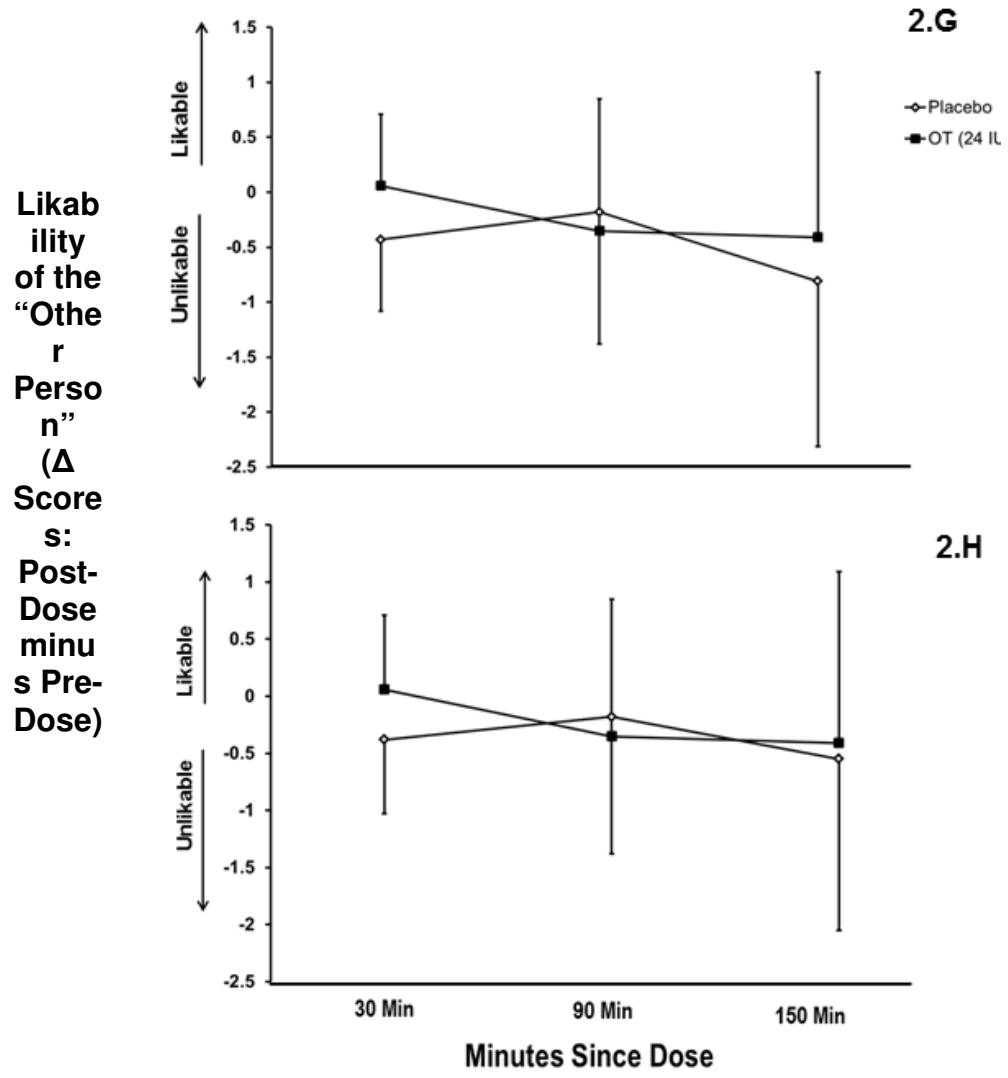
In subsequent exploratory analyses, raw Social VAS ratings (not converted into a difference score) were correlated with number of provocations, using all sessions and doses. To account for repeated measures, intraclass correlations coefficient (ICC) were calculated. No statistically significant correlation was found between raw Social VAS ratings and the number of provocations the participant experienced on the PSAP, r_{ICC} (136) = -0.14, p = 0.12, when the outlier in the Social VAS rating was present. There was no statistically significant correlation between raw Social VAS ratings and the number of provocations the participant experienced on the PSAP, r_{ICC} (135) = -0.17, p = 0.06, when the outlier in the Social VAS ratings was removed.

Minutes since dose (Post-Dose Session)	Placebo	OT (24 IU)
30 min (1)	-0.4 (0.9)	0.06 (0.65)
90 min (2)	-0.18 (1.3)	-0.35 (1.22)
150 min (3)	-0.81 (1.5)[1] -0.55 (1.2)[2]	-0.41 (1.3)

Table 2.H Descriptive statistics of Social VAS ratings (Δ scores) across all post-dose sessions for both doses.
Data are presented as mean (S.D) for all Social VAS ratings.
Superscript 1 refers to data with the outlier included. Superscript 2 refers to data without the outlier. (Δ scores: Post-Dose minus Pre-Dose).
IU = international unit.

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn-Feldtcorr)}$
Social VAS (Δ Scores)[1]					
	Main				
	Dose	(1, 16)	0.45	0.52	0.52
	Session	(2, 32)	2.51	0.09	0.09
	Interaction				
	Dose X Session	(2, 32)	2.16	0.13	0.13
Social VAS (Δ Scores)[2]					
	Main				
	Dose	(1, 16)	0.50	0.50	0.50
	Session	(2, 32)	2.02	0.15	0.15
	Interaction				
	Dose X Session	(2, 31)	1.98	0.13	0.13

Table 2.I Summaries of the RM ANOVAs on all Social VAS ratings (Δ scores).
Social VAS (Δ Scores)[1] refers to RM ANOVA model with the outlier in Social VAS rating data. Social VAS (Δ Scores)[2] refers to RM ANOVA model without the outlier in Social VAS rating data. $p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn-Feldtcorr)}$= corrected p-value for repeated measures. (Δ scores: Post-Dose minus Pre-Dose).



Figures 2.G and 2.H Social VAS ratings of "likability" across all post-dose sessions for both doses.
Presented are the Social VAS ratings over the course of three different post-dose time points (sessions) for both dose levels. Minutes since dose: 30 Min, 90 Min, and 150 Min represent Post-Dose Session 1, 2, and 3, respectively. All data are presented as mean (S.D.). Figure 2.G contains data with the outlier. Figure 2.H contains data without the outlier.
IU = international unit.

Cardiovascular data

All HR data (Δ scores) were examined using a two-way RM ANOVA testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and interaction of dose by session. The RM ANOVA found no statistically significant main effects of dose or any interaction of dose by session. When the outlier was present in the data, there was a statistically significant effect of session. However, when the outlier was removed from the data, there was no statistically significant effect of session.

All Systolic BP data (Δ scores) were examined using a two-way RM ANOVA testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and the interaction of dose by session. There were no statistically significant effects of dose or session. There was no statistically significant interaction of dose by session.

All Diastolic BP data (Δ scores) were examined using a two-way RM ANOVA testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and interaction of dose by session. A statistically significant main effect of dose was found both, when the outlier was present in the data and when the outlier was removed from the data. There were no statistically significant effects of session or interaction of dose by session. Figures 2.I and 2.J show Diastolic BP data (Δ scores) for OT and Placebo across all post-dose sessions with and without the outlier.

A statistically significant main effect of dose was found in the Diastolic BP data. Post-hoc analysis using Tukey's honest square difference (Tukey,

1949) on Diastolic BP data without the outlier indicated OT significantly decreased BP across all participants ($p = 0.05$). Descriptive statistics for all cardiovascular data for all sessions across both dose levels are provided in Table 2.J. Summaries of the results from all of the RM ANOVAs on all cardiovascular data (Δ scores) are provided in Table 2.K. Summaries of all raw cardiovascular data are found in the Appendix material.

Cardiovascular measure	Minutes since dose (Post-Dose Session)	Placebo	OT (24 IU)
HR (Δ Scores)			
	30 min (1)	-2.8 (9.3)[1] -4.7 (4.5)[2]	-2.9 (5.5)
	90 min (2)	-5.1 (5.2)	-4.2 (6.7)
	150 min (3)	-6.1 (8.5)	-4.6 (6.3)
Systolic BP (Δ Scores)			
	30 min (1)	3.9 (6)	-0.3 (6.8)
	90 min (2)	5.6 (7.8)	2.2 (4.7)
	150 min (3)	6.5 (6.5)	3.2 (6.4)
Diastolic BP (Δ Scores)			
	30 min (1)	4.1 (6)	0.2 (4.4)
	90 min (2)	5.6 (7.8)[1] 4.5 (5.3)[2]	1.1 (5.2)
	150 min (3)	4.4 (4.9)	2.8 (5.9)

Table 2.J Descriptive statistics of all cardiovascular data (Δ scores).
Data are presented as mean (S.D) for all cardiovascular data. Superscript 1 refers to data with the outlier. Superscript 2 refers to data without the outlier.
(Δ scores: Post-Dose minus Pre-Dose). IU = international unit.

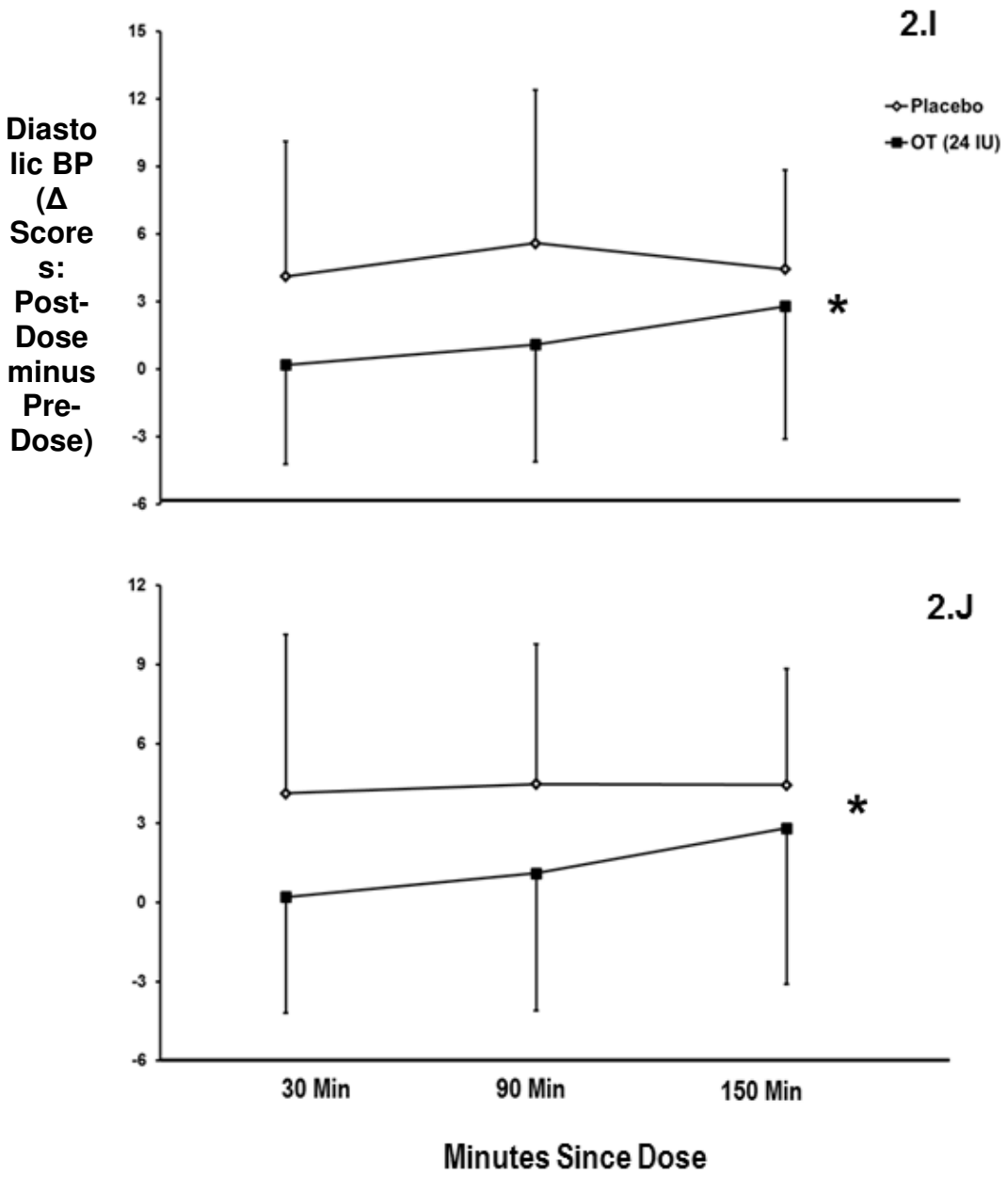
Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn\text{-}Feldtcorr)}$
HR (Δ Scores)[1]					
	Main				
	Dose	(1, 16)	0.16	0.69	0.69
	Session	(2, 32)	4.41	0.02	0.02
	Interaction				
	Dose X Session	(2, 32)	0.39	0.68	0.68
HR (Δ Scores)[2]					
	Main				
	Dose	(1, 16)	0.49	0.49	0.49
	Session	(2, 32)	2.05	0.14	0.14
	Interaction				
	Dose X Session	(2, 31)	0.07	0.93	0.93
Systolic BP (Δ Scores)					
	Main				
	Dose	(1, 16)	2.75	0.11	0.11
	Session	(2, 32)	1.64	0.2	0.2
	Interaction				
	Dose X Session	(2, 32)	1.76	0.18	0.18

Table 2.K Summaries of the RM ANOVAs on all cardiovascular data (Δ scores).
HR (Scores)[1] refers to RM ANOVA model with the outlier in the HR data.
HR (Scores)[2] refers to RM ANOVA model without the outlier in the HR data.
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn\text{-}Feldtcorr)}$= corrected p-value for repeated measures.
(Δ scores: Post-Dose minus Pre-Dose).

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn\text{-}Feldtcorr)}$
Diastolic BP (Δ Scores)^1					
	Main				
	Dose	(1, 16)	6.73	0.01	0.01
	Session	(2, 32)	0.83	0.44	0.44
	Interaction				
	Dose X Session	(2, 32)	1.02	0.37	0.37
Diastolic BP (Δ Scores)^2					
	Main				
	Dose	(1, 16)	4.51	0.04	0.04
	Session	(2, 32)	0.98	0.38	0.38
	Interaction				
	Dose X Session	(2, 31)	0.79	0.46	0.46

(Continued from the previous page)

Table 2.K Summaries of the RM ANOVAs on all cardiovascular data (Δ scores).
Diastolic BP (Scores)^1 refers to RM ANOVA model with the outlier in the Diastolic BP data.
Diastolic BP (Scores)^2 refers to RM ANOVA model without the outlier in the Diastolic BP data.
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn\text{-}Feldtcorr)}$= corrected p-value for repeated measures.
(Δ scores: Post-Dose minus Pre-Dose).



Figures 2.I and 2.J Diastolic BP (Δ scores) across three post-dose sessions for both doses.
Presented are the Diastolic BP over the course of three different post-dose time points (sessions) for both dose levels. All data are presented as mean (S.D.). * = $p<0.05$, main effect of dose. Minutes since dose: 30 Min, 90 Min, and 150 Min represent Post-Dose Session 1, 2, and 3, respectively. All data are presented as mean (S.D.). Figure 2.I contains data with the outlier. Figure 2.J contains data without the outlier.
IU = international unit. IU = international unit.

Body Temperature data

All BT data (Δ scores) were examined using a two-way RM ANOVA testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and the interaction of dose by session. The RM ANOVA found no statistically significant main effect of dose or session, or any interaction of dose by session. Descriptive statistics of BT data (Δ scores) across all sessions and both dose levels are presented in Table 2.L. Summary of RM ANOVA output on BT data (Δ scores) is found in Table 2.M.

Minutes since Dose (Post-Dose Session)	Placebo	OT (24 IU)
30 min (1)	-0.08 (1.08)	-0.46(1.04)
90 min (2)	-0.14 (1.19)	-0.13 (1.12)
150 min (3)	0.02 (1.36)	-0.33 (0.82)

Table 2.L Descriptive statistics of BT data (Δ scores).
Data are presented as mean (S.D.) of all BT data.
(Δ scores: Post-Dose minus Pre-Dose). IU = international unit.

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn\text{-}Feldtcorr)}$
BT (Δ Scores)					
	Main				
	Dose	(1, 16)	0.75	0.40	0.40
	Session	(2, 32)	2.26	0.12	0.12
	Interaction				
	Dose X Session	(2, 32)	0.13	0.87	0.87

Table 2.M Summary of the RM ANOVA on BT data (Δ scores).
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn\text{-}Feldtcorr)}$= corrected p-value for repeated measures.
(Δ scores: Post-Dose minus Pre-Dose).

POMS data

All POMS subscales scores (Δscores) were analyzed with seven separate two-way RM ANOVAs (one for each subscale) all testing for main effects of dose (Placebo vs OT) and session (sessions at 30, 90, and 150 min post-dose), and interaction of dose by session. For planned multiple comparisons of each POMS subscale (Δ scores), the Benjamini–Yekutieli false discovery rate (Benjamini & Yekutieli, 2001) was employed (to correct for multiple comparisons across the multiple subscales) in addition to the Huyn-Feldt corrected p-values. The Benjamini–Yekutieli false discovery rate determined that a critical p-value ($p < 0.003$) should be used to signify statistical significance.

After correction, a significant main effect of dose was found for the fatigue subscale of the POMS ($F(1, 16) = 9.05$, $p_{(uncorr)} = 0.002$, $p_{(corrHuyn\text{-}Feldt)} = 0.002$). Post-hoc analysis using Tukey's honest square difference (Tukey, 1949) indicated that under OT, participants reported less fatigue ($p = 0.05$), as compared to placebo.

The RM ANOVA found no other statistically significant main effects of dose, or session or any interaction of dose by session. Descriptive statistics of POMS subscale data averaged across all sessions are presented in Table 2.N. Summaries of the results from all RM ANOVAs on all POMS subscales (Δ scores) are found in Table 2.O. Descriptive statistics of all raw POM subscales by session and dose are in the Appendix material

Subscale	Placebo	OT (24 IU)
Depression-Dejection	0 (0.41)	-0.2 (0.5)
Vigor	-0.1 (2.8)	1.0 (3.4)
Confusion-Bewilderment	0.2 (0.5)	-0.1 (0.4)
Tension-Anxiety	0.1 (0.7)	0.2(1.3)[1] 0.1(0.8)[2]
Anger-Hostility	0.2 (0.6)	-0.1 (0.8)
Fatigue	0.8(1.5)	-0.6(1.6)

Table 2.N Descriptive summaries of all POMS subscales (Δ scores). Data are presented as mean (S.D) from all POMS subscales. Superscript 1 represents data with the outlier. Superscript 2 represents data without the outlier. (Δ scores: Post-Dose minus Pre-Dose). IU = international unit.

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn\text{-}Feldtcorr)}$
Depression-Dejection (Δ Scores)					
	Main				
	Dose	(1, 16)	1.38	0.26	0.26
	Session	(2, 32)	0.58	0.57	0.54
	Interaction				
	Dose X Session	(2, 32)	0.94	0.40	0.37
Vigor (Δ Scores)					
	Main				
	Dose	(1, 16)	9.05	0.008	0.008
	Session	(2, 32)	0.37	0.69	0.63
	Interaction				
	Dose X Session	(2, 32)	1.49	0.24	0.24
Confusion-Bewilderment (Δ Scores)					
	Main				
	Dose	(1, 16)	4.31	0.54	0.54
	Session	(2, 32)	4.12	0.03	0.03
	Interaction				
	Dose X Session	(2, 32)	0.71	0.50	0.50

Table 2.O Summaries of the RM ANOVAs on all POMS data (Δ scores)
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn\text{-}Feldtcorr)}$= corrected p-value for repeated measures. (Δ scores: Post-Dose minus Pre-Dose).

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn-Feldtcorr)}$
Tension-Anxiety (Δ Scores)[1]					
	Main				
	Dose	(1, 16)	0.20	0.66	0.66
	Session	(2, 32)	0.73	0.49	0.48
	Interaction				
	Dose X Session	(2, 32)	3.15	0.06	0.08
Tension-Anxiety (Δ Scores)[2]					
	Main				
	Dose	(1, 16)	0.09	0.77	0.77
	Session	(2, 32)	0.15	0.86	0.86
	Interaction				
	Dose X Session	(2, 31)	2.78	0.07	0.08

Continued from the previous page

Table 2.O Summaries of the RM ANOVAs on all POMS data (Δ scores)
Tension-Anxiety (Scores)[1] refers to RM ANOVA model with the outlier in the Tension-Anxiety data.
Tension-Anxiety (Scores)[2] refers to RM ANOVA model without the outlier in the Tension-Anxiety data.
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn-Feldtcorr)}$= corrected p-value for repeated measures.
(Δ scores: Post-Dose minus Pre-Dose).

Dependent Variable	Effect	(df)	F-score	$p_{(uncorr)}$	$p_{(Huyn-Feldtcorr)}$
Anger-Hostility (Δ Scores)					
	Main				
	Dose	(1, 16)	1.31	0.27	0.27
	Session	(2, 32)	3.33	0.04	0.08
	Interaction				
	Dose X Session	(2, 31)	0.16	0.85	0.71
Fatigue (Δ Scores)					
	Main				
	Dose	(1, 16)	12.97	0.002	0.002**
	Session	(2, 32)	2.64	0.08	0.09
	Interaction				
	Dose X Session	(2, 32)	0.32	0.73	0.73

Continued from the previous page

Table 2.O Summaries of the RM ANOVAs on all POMS data (Δ scores)
$p_{(uncorr)}$ = uncorrected p-value. $p_{(Huyn-Feldtcorr)}$= corrected p-value for repeated measures.
** = statistically significant after false discovery rate correction.
(Δ scores: Post-Dose minus Pre-Dose).

Post-Hoc Power analysis

This experiment was modelled after previous studies of OT using similar numbers of participants (Bakermans-Kranenburg & van IJzendoorn, 2013; Bethlehem et al., 2013) and previous studies using the PSAP methodology (Cherek et al, 2003; 2006). A post-hoc power analysis was conducted using Gpower 3.3, to provide post-hoc power estimates based on obtained effect sizes from the data. Table 2.P presents all effect sizes for all aims and their associated obtained power.

Aim	Effect size	Obtained power
2a: Aggressive Response Rate (Average) with outlier	Cohen's d = 0.21	0.12
2a: Aggressive Response Rate (Average) without outlier	Cohen's d = 0.14	0.08
2a: Aggressive Response Rate (Peak Effect)	Cohen's d= 0.11	0.07
2b: Personality Traits and Aggression	Cohen's f^2= 0.49	0.77
2c: Social VAS ratings with outlier	Cohen's d= 0.16	0.09
2c: Social VAS ratings without outlier	Cohen's d= 0.15	0.08

Table 2.P Summary of post-hoc power analyses from the data.

Discussion

The goal of Experiment 2 was to test if OT decreases human aggressive behavior. This experiment was designed to reduce the intra-subject and inter-subject variability that was observed in Experiment 1 (chapter 2). In the previous experiment (chapter 2), changes in aggressive responding under OT were observed; however, these changes in aggressive responding were neither systematic nor orderly. This experiment was designed to reduce subject variability in an attempt to (i) test the hypothesis that OT would reduce aggressive behavior and (ii) elucidate the direction of change in aggressive behavior following OT dosing. No statistically significant main effect of OT on aggression was found. The hypothesis that acute OT administration reduces aggressive behavior was not supported.

Interestingly, there was a broad range of changes in aggressive responding on the PSAP under OT. Some participants increased their aggressive responding, whereas other participants decreased their aggressive responding under OT, suggesting (as in Experiment 1) individual differences played a role in moderating the effects. A positive correlation between the personality traits of interpersonal manipulation + anger and aggressive responding following OT dose was observed. This result is contrary to the hypothesized direction, in which it was predicted that those with highest levels of antisocial traits would show the greatest reductions. This finding suggests that these antisocial personality traits (interpersonal manipulation and anger) might moderate the effects of OT on aggression. A study design that examined

the role of those two personality factors in a moderation- or mediation-based design (which would require a much larger sample size) could address this hypothesis more directly.

If replicated and extended, this result may be clinically important because interpersonal manipulation and anger are key indicators of antisocial behavior. Alcorn III et al. (2013) found that psychopathic and aggressive personality traits were two key psychometric measures that identified ASPD+SUD individuals from SUD alone and healthy volunteers. Thus, by extension, OT may increase aggressive behavior in individuals who share personality traits consistent with ASPD+SUD groups. Additionally, this result could explain some of the variability observed in Experiment 1, in which increases in aggressive responding were observed in some participants following OT administration in ASPD+SUD. However, this reasoning is speculative, and systematic replication of Experiment 1 using the design of this experiment would be needed to confirm this idea. Another interpretation of the positive correlation between interpersonal manipulation + anger and aggressive responding under OT is the possibility of a group by dose interaction. To fully test this notion, individuals who meet full diagnostic criteria for comorbid ASPD+SUD and healthy controls would need to be tested using the design of Experiment 2, using pre-dose and post-dose sessions, and the same psychometric questionnaires (e.g., interpersonal manipulation and anger). The hypothesis would be that ASPD+SUD individuals would increase in their aggressive responding following administration whereas healthy volunteers

(with lower interpersonal manipulation/anger) would decrease or show no change in their aggressive responding under OT.

There are precedents in the OT and aggression literature to suggest a group by dose interaction. Winslow & Insel (1991) found that in squirrel monkeys, behavioral responses (aggressive displays, sexual behavior, and approach behavior) following central administration of OT depend on dominance status. In dominant but not subordinate squirrel monkeys, aggressive, sexual, and approach behavior to a conspecific was increased following central administration of OT. Additionally, these behavioral responses in dominant squirrel monkeys were blocked following administration of an antagonist of OT. Similarly, Bartz et al. (2010) compared trust and cooperative behavior following OT administration in borderline personality disordered individuals (BPD) and healthy volunteers and found a significant group by dose interaction. Bartz et al. (2010) reported that BPD individuals receiving OT exhibited decreased levels of trust and cooperative behavior, whereas higher levels of trust and cooperative behavior were observed in healthy volunteers. Group by dose interactions have also been reported in aggressive responding. Cherek et al. (2002b) reported that, compared to individuals with a history of conduct disorder (CD), individuals without a history of CD increased in their aggressive responding on the PSAP following acute administration of baclofen, a gamma-aminobutyric acid-B agonist; individuals with a history of CD actually decreased aggressive responding on the PSAP following acute administration of baclofen.

Experiments 1 and 2 provide an initial suggestion that individual differences in antisocial personality traits modulate to human aggressive responding following acute OT administration. Experiment 2 provides insight about which target individual differences to be considered for future research in this area.

There was not a statistically significant main effect of OT on ratings of likability. OT dose did not alter social judgments of the “other person” following interactions on the PSAP. The rationale for measuring ratings of “likability” was to test if OT changed social judgment of the “other person” following a social interaction that elicits aggressive responding. Thus, this aim was proposed in order to elucidate a possible source of socio-cognitive variability that could have occurred under OT and possibly be related to aggressive behavior. However, there was no effect of OT on social cognition within this experiment and changes in aggressive behavior following OT were not associated with changes in social judgment.

Unlike Experiment 1, Experiment 2 OT significantly reduced BP in participants. This result provides confirmation that OT was biologically active, as previous literature has also reported decreases in BP following OT administration (Petersson et al., 1996; Rosseland et al., 2013). The discrepancy in a main effect of OT on diastolic BP could be related to the fact that ASPD+SUD populations have reduced resting cardiovascular functioning (Lorber, 2004; Patrick, 2008) or to altered blood pressure in substance abuse

populations (Dickley et al., 2002), or to differences in sample sizes between the two experiments.

Experiment 2 found a statistically significant main effect of OT on decreasing fatigue. Previous studies in both healthy and clinical populations have reported changes in mood following OT. Healthy participants under OT reported decreased ratings of vigor on the POMS following a visual memory task (Bruins et al., 1992) and alcoholic patients undergoing detoxification reported decreased ratings of tension and anxiety on the POMS following OT dosing (Pedersen et al., 2013). Thus, across different contexts, dose related changes in mood have been reported. However, given that there were no statistically significant main effects of OT on participant's behavior or social judgments in this experiment, the context in which dose related decreases in fatigue occurred is unclear. Future investigations are needed to appropriately identify possible controlling variables in dose related changes in mood.

This experiment has several limitations that impact interpretation of the results. First, for the majority of the data collected, the calculated effect sizes are small (range: 0.11 - 0.49). A meta-analytic study of OT effects conducted by Bakermans-Kranenburg & van IJzendoorn (2013) found small to moderate effect sizes (Cohen's d: 0.2 - 0.5), comparing OT to placebo dose in various disorders ranging from autism-spectrum to social anxiety to schizophrenia. Sources of the discrepancies between these moderate effects sizes and the small effect size obtained in this study are unclear, but may relate to measurement techniques and/or study design. Additional limitations relate to

the positive correlation found between personality traits of interpersonal manipulation + anger, and aggressive behavior under OT. This correlation was found in a non-clinical sample using combined scores of these two personality traits. Generalizability of this finding to ASPD+SUD populations should be cautious as additional research with these individuals is needed to appropriately address this issue. These personality traits (anger and interpersonal manipulation) were selected based on a statistical profile ASPD+SUD individuals in Alcorn III et al. (2013) as well as previous studies in clinical populations (Alia-Klein et al., 2009; Vaillancourt & Sunderani, 2011). However, this combination of personality traits does not have an established cut-off score that would distinguish clinically relevant groups. Thus, these personality traits are a proxy for antisocial characteristics rather than clinical marker of ASPD+SUD pathology.

Another limitation of Experiment 2 relates to the limited dose range. This experiment used one dose level (24 IU) which was the middle dose for Experiment 1 and a commonly used dose level in OT studies (Bakermans-Kranenburg & van IJzendoorn, 2013; Shahrestani et al., 2013). Future studies examining individual differences in acute OT effects on aggression and other antisocial behaviors should test across a full does range (when logistically feasible). Additionally, Experiment 2 provided no biological index (e.g., CNS or peripheral markers of OT levels) following intranasal administration. Currently, there are no pharmacokinetic data about the absorption and distribution of neuropeptides following intranasal administration. The best approximation in

these data is the main effect of OT dose on BP. This is a limitation of intranasal administration procedures due to uncertainty around OT levels actually present in the CNS during testing. Lastly, both experiment 1 and 2 are limited to aggressive behavior under OT in males. The present experiments do not address gender effects with OT.

Collectively, the results of Experiment 2, (i) extend the data of acute OT effects in relation to moderating social behavior, (ii) elucidate sources of individual differences related to aggressive behavior in the context of the OT; and (iii) tentatively suggest that OT may not be an efficacious therapeutic for managing aggression in individuals with antisocial traits or diagnosis of ASPD+SUD.

CHAPTER 4: DISCUSSION AND FUTURE DIRECTIONS

Concluding commentary on Experiments 1 and 2:

The goal of this dissertation was to examine the effects of oxytocin (OT) on human aggression. Aggression represents a class of antisocial behavior that is particularly prevalent in individuals with Antisocial Personality Disorder (ASPD) and substance abuse (Allen et al., 1997; Moeller et al., 1998; APA, 2000; Alcorn III et al., 2013). Aggression in these individuals can manifest at maladaptive levels that place a burden on society and public health systems. The overarching hypothesis of this dissertation was that OT would decrease aggressive behavior. This hypothesis was tested in two different experiments but was not supported. The experiments of this dissertation provide limited information about the association between OT and human aggression and suggest that personality traits may be a factor in predicting individual differences in response to OT.

The goal of Experiment 1 was to test the hypothesis that OT decreases aggression in ASPD and substance use disordered (SUD) participants, and to potentially provide an indication of which OT dose level would provide the biggest reduction in aggression. Experiment 1 was the first study to test if OT would dose-dependently decrease aggression in a clinically relevant population, across a range of doses. The hypothesis of Experiment 1 was not supported. Data from Experiment 1 suggested that the experimental design was susceptible to high intra-subject and inter-subject variability which prevented clear conclusions about the direction and magnitude of OT dosing on aggressive behavior. In order to better understand individual differences, a

single subject data analytic approach was conducted. At the single-subject level, an exploratory analysis of inter-response time (IRT) distributions in aggressive responding was conducted in conjunction with the primary dependent measure of overall aggressive response rate (i.e. aggressive responses per minute). Experiment 1 was the first study to analyze IRT distributions of aggressive responding on the Point Subtraction Aggression Paradigm (PSAP). The decision to analyze IRT distributions was motivated by the possibility that IRT distributions could reveal information about OT on aggression. IRT analyses provide information at fine-grained temporal resolution; this information is unique from the overall response rate. Across both levels of behavioral analysis (i.e. overall aggressive response rate and IRT distributions), changes in aggressive responding following OT administration were observed. However at both levels of analysis, these changes in aggressive responding were neither orderly nor systematic across participants, and in some instances not within the same participant. Experiment 1 concluded that observed changes in behavior under OT were specific to aggression (a social behavior) and were not a product of stimulation or sedation from OT administration. Support for these conclusions was provided by the observation that there were few changes in monetary-reinforced responding (non-social behavior), which occurs at a high rate and indexes motor coordination. However, the variability that was dose related could not be distinguished from non-experimental sources of variability, such as shifts in baseline responding. Additionally, identification of any variability related to individual differences (e.g.,

ASPD characteristics, specific drug of abuse, and history of violence) could not be identified in the data. The conclusions in Experiment 1 were therefore restricted to qualitative rather than quantitative interpretations.

To overcome the intra-subject and inter-subject variability of Experiment 1 in ASPD+SUD participants, Experiment 2 was designed to reduce variability in order to test the hypothesized effects of OT on aggressive behavior. The hypothesis of Experiment 2 was that OT administration will reduce aggressive behavior. In addition to testing the hypothesis under more stringent experimental control, Experiment 2 explored whether personality traits related to aggression in the context of ASPD+SUD (e.g., interpersonal manipulation and anger, Alcorn III et al., 2013) were related to changes in aggression under OT. In addition to testing aggression, a sub-hypothesis of Experiment 2 was that OT would increase prosocial judgment of the “other person” in the Point Subtraction Aggression Paradigm (PSAP). The rationale for this aim was based on prior evidence from human and non-human studies that OT increases prosocial cognition (Domes et al., 2007a; Guastella et al., 2008; 2010) and affiliative behaviors towards a conspecific (Carter et al., 2008; Lee et al., 2009a; Williams et al., 1994).

Experiment 2 reduced intra-subject sources of variability by establishing stable baseline responding before each dose. However, there were no statistically significant main effects of OT on aggressive behavior or social judgment. Instead, there was higher than anticipated levels of between subject variability following OT dosing, which suggesting individual differences may

have influenced the results. The aim of examining personality traits was to identify a source of variability that might be significantly associated with aggression under OT. Correlational analysis of interpersonal manipulation and anger personality traits and aggression under OT revealed a statistically significant positive association; individuals who reported higher levels of interpersonal manipulation + anger were positively correlated with higher levels of aggressive behavior. Importantly, these two personality traits are part of a constellation of clinically relevant personality factors that statistically identify ASPD+SUD individuals from SUD only and healthy volunteers (Alcorn III et al., 2013). In relating the results of Experiment 2 to the goals of Experiment 1, this positive association between interpersonal manipulation + anger and aggressive behavior under OT suggests that OT may not be an efficacious therapeutic for treating aggression observed in populations characterized by those traits (e.g., ASPD and SUD). The results of Experiment 2 (i) provided information that could be used for further investigations of OT on antisocial behavior, and (ii) identified a source of individual difference variability that may be relevant for understanding the clinical utility of OT as a therapeutic.

There are two differences in data analysis between Experiments 1 and 2. First, IRT distributions were not analyzed in Experiment 2. The rationale for not including analysis of IRT distributions in Experiment 2 is that analysis of IRT distributions is restricted to single subject level and statistical comparisons pooled from data across participants are not meaningful (Iversen, 1991; Payla, 1992). A second difference in data analysis between Experiment 1 and

Experiment 2 relates choosing the peak effect. In Experiment 1, the pharmacological peak effect was chosen because there were no orderly or systematic effects of OT on aggressive behavior across sessions or participants. Therefore, the session conducted 90 minutes after dose administration was chosen as the pharmacological peak effect because this time point approximates the average post-dose time point in which neuropeptides reach their highest level of central nervous system (CNS) accumulation in humans (Born, 2002). The peak effect in Experiment 2 was identified behaviorally, because there was a baseline (pre-dose) session from which the maximal change in aggressive responding following OT dose could be identified. This allowed for the possibility of individual differences in the time course of biological and psychological effects across participants, which are commonly seen in behavioral pharmacology (Cherek & Lane, 2001; Lane et al., 2008; Lane & Gowin, 2009; Rush et al., 2011; Sevak et al., 2009; Stoops et al., 2008).

Experiments 1 and 2 provide unique types of information about aggressive behavior following acute OT administration. Neither experiment was consistent with the overall hypothesis but each identified statistically significant individual differences in response to OT that were specific to aggressive behavior. These differences were observed both via confirmatory and exploratory data analytic approaches. Confirmatory and exploratory data analyses are two methods of conducting research, and when used together

provide a broader understanding of data that is important for understanding and furthering scientific investigation (Tukey, 1980).

Aggression and Oxytocin

The rationale for the overall hypothesis of this dissertation follows from the "prosociality model of OT function" (Ebitz & Platt, 2014). In this model, endogenous release of OT or exogenous administration of OT during a social interaction is thought to promote the generation of prosocial behaviors in response to social signals from conspecifics. Given that aggression is characterized, in part, by social behaviors that are opposite to prosocial behavior, it was predicted that aggression following OT dosing should decrease. In Experiments 1 and 2, there were individuals whose aggressive behavior under OT followed in the predicted direction (i.e., their aggressive behavior decreased under OT). However, aggressive behavior across all individuals did not systematically follow this model's predicted direction. In Experiments 1 and 2, there were individuals whose aggressive behavior increased following OT dosing. The prosociality model of OT function does not account for effects of OT dosing that increase the aggressive behavior of these individuals. Thus, a limitation of this model is that it does not account for instances in which OT administration results in behavior that is not prosocial.

There is some evidence in both human and non-human animal literature which to suggesting that OT does not always promote prosocial behavior. For example, Shamay-Tsoory et al. (2009) found that OT administration increased

schadenfreude (gloating at the expense of others) in human participants when monetary losses were incurred to another (fictitious) person. Bartz et al., (2010) found that OT diminishes cooperation and trust in individuals with borderline personality disorder (BPD). Chang et al. (2012) found that in rhesus monkeys, OT increased selfish choices when monkeys were faced with the choice of either giving a reward to itself or to another monkey. De Dreu (2012) reported increased threat perception of individuals from other groups following OT administration. To account for the contexts in which OT does not uniformly engender prosocial behavior, Ebitz & Platt (2014) proposed "the adaptive component process model of OT function". According to the adaptive component process model of OT function, endogenous release or exogenous delivery of OT engenders social behavior patterns that are adaptive in response to perceived signals from conspecifics during social interactions. OT increases prosocial behavior in contexts when prosocial behavior is perceived by the organism to be adaptive and reduces prosocial behavior in contexts when it is not perceived by the organism to be adaptive. In this model, behavioral responses following OT release or administration can vary across different individuals and contexts. The adaptive component process model also describes the variation in the activity of the OT system with respect to variation in social behavior. For example, prairie voles are a monogamous rodent species that form pair-bonds dependent on the endogenous release of OT following mating (Williams et al., 1994). There is a related vole species called meadow voles that are polygamous and do not form pair-bonds following

mating. Insel & Shapiro (1992) demonstrated that prairie voles had higher densities of the OT receptor in their nucleus accumbens (NAcc) and prelimbic cortex (PLC) compared to meadow voles. The adaptive component process model states that in prairie voles, affiliative signals following mating result in the endogenous release of OT, which in turn activates reward processing circuitry in the NAcc and PLC to form pair-bonds. Since meadow voles have lower densities of OT receptors in their NAcc and PLC compared to prairie voles, pair bonds don't form in meadow voles when OT is released during the same interaction (i.e., mating). Thus, the adaptive component process model of OT function can account for variation in social behaviors following OT administration and release. However, the adaptive component process model of OT function does not directly model OT in the context of aggressive behavior in psychiatric groups, or how expression of aggressive behavior following OT would vary across individuals. It is possible, however, that humans have (a) greater variation in expression of both OT and OT receptor density and (b) greater variation in complexity and history of social interactions. These factors may have contributed to the variation among participants in the present experiments, and would in this extended manner, be consistent with the notions posited by the adaptive component process model of OT function.

In the context of human aggression, the general aggression model (GAM) posits cognitive and emotional variables within a person that lead to aggressive acts. For example, the GAM describes how individuals, who experience more anger, are more likely to express acts of aggression in

response to provocation (Anderson & Bushman, 2002). Within the context of Experiment 2 of this dissertation, anger was identified as a predictor of aggressive behavior following OT administration. In Experiment 2, individuals with higher anger related personality traits increased in their aggressive behavior under OT. However, the GAM is a theoretical model that broadly accounts for the episodes of human aggression, and does not make specific predictions regarding OT or other biochemical systems.

Aggression is a social behavior mediated in part by the OT system. Given that in Experiments 1 and 2 there were instances of increased aggression following OT administration in some individuals but not in others, future studies OT in human aggressive behavior should consider individual differences related to both personality and biological factors .

Future Directions

This dissertation provides a small step in examining aggression and its relation to the OT system. The experiments reported individual differences in aggression following OT administration. Future investigations of individual differences (using a biopsychosocial model) could examine biological variables in conjunction with personality variables. For example, examining the interaction between endogenous levels of testosterone, psychopathic and anger traits, and OT may help explain the variability in aggression following OT administration. Winslow & Insel (1991) reported that central administration of OT resulted in increased aggression in dominant squirrel monkeys but not subordinate squirrel

monkeys. Winslow & Insel (1991) also reported that dominant squirrel monkeys had higher levels of testosterone compared to subordinate squirrel monkeys. Since (a) higher levels of testosterone have been known to predict aggression in both humans and non-humans (Archer, 2004; Soma, 2006; Carré et al., 2011) and (b) higher levels of testosterone are found in individuals with persistent antisocial behavior (Yildirim & Derksen, 2012a) and individuals with interpersonal affective deficits (Yildirim & Derksen, 2012b), future studies should test if baseline differences in levels of testosterone predict aggression following OT administration. Such a study could follow from Experiment 2 of this dissertation, since psychopathic and aggressive personality traits were associated with increased aggression under OT, and these traits are prevalent in antisocial individuals (Alcorn III et al., 2013; Nouvion et al., 2007) who are also reported to have higher levels of testosterone (Yildirim & Derksen, 2012a).

Another future direction would be to examine the interaction between serotonin (5-hydroxytryptamine; 5-HT) and OT administration in aggression. In this dissertation, some individuals showed decreased aggression following OT administration. 5-HT is a known modulator of aggression in both human and non-human animal species and decreased central levels of serotonin are associated with increased levels of aggression (Higley et al., 1992; Krakowski, 2003; Mehlman et al., 1994; Moore et al., 2002). Levels of 5-HT could interact with OT and may help explain the variability in aggression following OT administration. Krakowski (2003) suggested that 5-HT is an important modulator for social bonds. Dölen et al. (2013) reported that the processing of

social rewards during rodent social interaction requires coordinated activity from OT and 5-HT. Given that administration of drugs that increase 5-HT transmission are known to decrease human aggressive behavior (Cherek & Lane, 1991, 2001; Cherek et al., 2002a; Gowin et al., 2010) and increase feelings of sociability (Kirkpatrick et al., 2014), it is possible that OT could interact with baseline levels of 5-HT. Specifically, in individuals with higher baseline levels of 5-HT, OT might actually decrease aggression. By contrast, in those with high baseline levels of testosterone, OT might increase aggression.

Future studies also could examine associations between aggression and variation in the OT receptor gene. One key target is the C allele of the OT receptor gene single nucleotide polymorphism (SNP) rs1042778. Malik et al. (2012) found that males with a history of childhood-onset aggression had a 2.5 fold over-representation of the C allele in the SNP rs1042778, compared to males who had no history of childhood-onset aggression. Interestingly, in this sample of individuals with childhood-onset aggression, 83% met diagnostic criteria for a history of conduct disorder, which is a childhood disorder required to precede full diagnostic criteria for ASPD in adulthood (APA, 2000). Given that antisocial personality traits accounted for part of the individual difference variability in aggression following OT administration in Experiment 2, the allelic expression of SNP rs1042778 could be an additional source of individual difference variability in the expression of aggression following OT administration.

Lastly, an important future direction is the impact of childhood trauma in mediating or moderating effects of OT on human aggressive behavior. Studies with rhesus monkeys showed that rearing conditions modulated CNS expression of OT. Specifically, Winslow et al (2003) observed that lower cerebral spinal fluid levels of OT were found in rhesus monkeys that were not maternally reared, compared to those that were maternally reared. The rhesus monkeys that were not maternally reared also showed higher displays of aggressive behavior compared to those that were maternally reared. Childhood trauma is known to be a predictor of emotional response to affective stimuli following OT, and a predictor for later violence (Widom, 1989). In individuals with BPD, the acute effects of oxytocin on stress reactivity were predicted by childhood trauma (Simeon et al., 2011). Specifically, in individuals with BPD who were given an acute OT dose, emotional response to stress was attenuated, and childhood trauma was the strongest predictor of oxytocin's attenuation of the emotional response to stress. Regarding the association between childhood trauma and aggression, Gowin et al. (2013) found that a history of childhood trauma was a significant predictor of increased aggressive behavior. The elucidation of relationships among childhood trauma, OT, and aggression appears warranted.

The suggested studies could provide information about individual differences in biological factors and personality traits, and personal history that would provide excellent tests of the adaptive component process model of OT function (Ebitz & Platt, 2014).

Conclusion

In conclusion, Experiments 1 and 2 revealed substantial individual differences in aggression following OT administration. Unfortunately, the directional hypothesis that OT would systematically decrease aggression was not supported. These experiments indicate that further information regarding variables that influence acute OT effects are required before conclusions can be reached about the utility of OT in the management of aggression.

APPENDIX MATERIAL FOR EXPERIMENT 1 (CHAPTER 2)

A1.A Summary of the behavioral data from the PSAP

Aggressive Response Rate

Minutes Post-Dose (session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
30 min (1)	7.5 (4.7)	7.49 (2.7)	6.04 (3.2)	10.05 (3.4)
90 min (2)	9.58 (4.6)	6.94 (5.7)	9.96 (6.3)	11.07 (6)
150 min (3)	8.46 (2.9)	8.58 (4.8)	12.11 (9.2)	10.1 (4.4)
210 min (4)	13.3 (8.4)	13.88 (8.1)	10.13 (5.3)	8.63 (1.6)

Mean (S.D.) on the aggressive response option (responses per minute) for each dose and each PSAP session.
Taken from Alcorn III et al. (In Press)

Monetarily-reinforced Response Rate

Minutes Post-Dose (session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
30 min (1)	4.54 (0.5)	4.57 (0.3)	4.59 (0.5)	4.1 (0.7)
90 min (2)	4.49 (0.5)	4.45 (0.5)	4.62 (0.3)	4.08 (0.7)
150 min (3)	4.75 (0.6)	4.76 (0.4)	4.41 (0.3)	4.64 (0.8)
210 min (4)	4.5 (0.4)	4.58 (0.4)	4.6 (0.4)	4.53 (0.8)

Mean (S.D.) on the monetary-earning response option (responses per second) for each dose and each PSAP session.
Taken from Alcorn III et al. (In Press)

A1.B Descriptive summaries of Inter-Response Times

Median (Inter-Quartile Range) Inter-response Times in milliseconds for each participant at each dose on the aggressive response option. Data are presented from session 2 (90min Post-Dose).

Subject	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
s13121				
Median (IQR)	172 (156-188)	172 (156-187)	156 (141-187)	172 (157-203)
Range	125-578	110-484	94-437	125-515
s13146				
Median (IQR)	187(172-188)	157 (141-172)	a	172 (171-188)
Range	110-580	109-515		110-391
s13214				
Median (IQR)	328 (297-359)	250 (234-297)	281 (250-343)	266 (265-297)
Range	218-579	156-563	172-578	218-453
s13234				
Median (IQR)	172 (156-172)	172 (156-187)	187 (172-203)	187 (172-203)
Range	125-218	140-203	140-250	78-469
s13246				
Median (IQR)	187 (171-203)	172 (156-188)	172 (156-188)	172 (156-202)
Range	109-578	110-578	109-548	109-516
s13285				
Median (IQR)	172 (172-187)	219 (219-250) [b]	188 (172-188)	172 (156-175)
Range	156-219	218-250[b]	156-220	141-188

a = 24 IU dose data lost for this subject due to hardware malfunction
b = session for this subject was 15 min instead of 25 min, due to experimenter error.
Taken from Alcorn III et al. (In Press)

A1.C summaries of cardiovascular data

Heart Rate Data

Minutes since Dose (session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
-30 min	80.16 (10.7)	77.33 (11.3)	81.6 (13.7)	80 (15.7)
30 min (1)	72.33 (11.5)	68.5 (8.7)	74.76 (11.7)	70.5 (15.7)
90 min (2)	68.83 (10.8)	65.16 (9.6)	72 (12.6)	67.5 (11.3)
150 min (3)	67.5 (6.6)	63.8 (9.4)	67.1 (10.3)	66.5 (10.8)
210 min (4)	65.4 (8.1)	61.2 (7.5)	68 (12.5)	66.6 (11.3)

Mean (S.D.) on the Heart Rate (beats per minute) for each dose and each session. Minutes since dose (-30 refers to the Pre-Dose values. 30, 60, 150, 210 min, refer to sessions 1, 2, 3, 4, respectively). IU =international unit. Taken from Alcorn III et al. (In Press)

Systolic Blood Pressure Data

Minutes since Dose (session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
-30 min	114 (10.6)	115.66 (14.3)	116.5 (11.7)	116 (10.4)
30 min (1)	118 (11)	116.5 (11.2)	118.8 (8.1)	117 (7.9)
90 min (2)	114 (11.8)	118 (10.9)	118 (8.2)	123.8 (8.4)
150 min (3)	115 (8.9)	119 (12.8)	119 (9.8)	120.3 (11.8)
210 min (4)	121(9.7)	119 (7.9)	123 (8.3)	115 (8.7)

Mean (S.D.) on the Systolic Blood Pressure (mmHG) for each dose and each session. Minutes since dose (-30 refers to the Pre-Dose values. 30, 60, 150, 210 min, refer to sessions 1, 2, 3, 4, respectively). IU =international unit. Taken from Alcorn III et al. (In Press)

Diastolic Blood Pressure Data

Minutes since Dose (session)	Placebo	OT (12 IU)	OT (24 IU)	OT 48 (IU)
-30 min	75.16 (5.9)	77.8 (9.9)	75.5 (11.5)	76.8 (8.8)
30 min (1)	75.16 (10.5)	78.1 (8.2)	75.5 (9.5)	77.5 (7.1)
90 min (2)	76.66 (9.2)	78 (8.6)	80 (7.9)	78.6 (8.2)
150 min (3)	75.66 (6.4)	77 (7.5)	77.8 (8.9)	77.1 (9.7)
210 min (4)	79.2 (9.2)	76.8 (4.3)	80.6 (10.5)	76.4 (9.4)

Mean (S.D.) on the Diastolic Blood Pressure (mmHG) for each dose and each session. Minutes since dose (-30 refers to the Pre-Dose values. 30, 60, 150, 210 min, refer to sessions 1, 2, 3, 4, respectively). IU =international unit.
Taken from Alcorn III et al. (In Press)

A1.G Psychometric total scores for all ASPD+SUD participants.

Participant	SRP-III	BPAQ	BIS-11	IPAS-IA	IPAS-PM
s13121	196	69	52	29	30
s13146	169	77	63	27	24
s13214	184	52	70	31	29
s13234	166	88	61	39	22
s13246	205	88	76	37	23
s13285	178	88	67	22	28

SRP-III = Self Report of Psychopathy Scale – III Total Score; BPAQ = Buss-Perry Aggression Questionnaire Total Score; BIS-11 = Barratt Impulsiveness Scale – 11 Total Score; IPAS-IA = Impulsive Premeditated Aggression Scale – Impulsive Subscale Total Score; IPAS-PM = Impulsive Premeditated Aggression Scale – Premeditated Subscale Total Score.
Taken from Alcorn III et al. (In Press)

A1.H Psychometric Measures.

Self-Report of Psychopathy –III (SRP-III)

Please rate the degree to which you agree with the following statements about you. You can be honest because your name will not be connected to these answers.

1	2	3	4	5
Disagree Strongly	Disagree	Neutral	Agree	Agree Strongly

1. I□m a rebellious person.
2. I□m more tough-minded than other people.
3. I think I could "beat" a lie detector.
4. I have taken illegal drugs (e.g., marijuana, ecstasy).
5. I have never been involved in delinquent gang activity.
6. I have never stolen a truck, car or motorcycle.
7. Most people are wimps.
8. I purposely flatter people to get them on my side.
9. I□ve often done something dangerous just for the thrill of it.
10. I have tricked someone into giving me money.
11. It tortures me to see an injured animal.
12. I have assaulted a law enforcement official or social worker.
13. I have pretended to be someone else in order to get something.
14. I always plan out my weekly activities.
15. I like to see fist-fights.
16. I□m not tricky or sly.
17. I□d be good at a dangerous job because I make fast decisions.
18. I have never tried to force someone to have sex.
19. My friends would say that I am a warm person.
20. I would get a kick out of „scamming□ someone.
21. I have never attacked someone with the idea of injuring them.
22. I never miss appointments.
23. I avoid horror movies.
24. I trust other people to be honest.
25. I hate high speed driving.
26. I feel so sorry when I see a homeless person.
27. It's fun to see how far you can push people before they get upset.
28. I enjoy doing wild things.
29. I have broken into a building or vehicle in order to steal something or vandalize.
30. I don□t bother to keep in touch with my family any more.
31. I find it difficult to manipulate people.
32. I rarely follow the rules.
33. I never cry at movies.

34. I have never been arrested.
35. You should take advantage of other people before they do it to you.
36. I don□t enjoy gambling for real money.
37. People sometimes say that I□m cold-hearted.
38. People can usually tell if I am lying.
39. I like to have sex with people I barely know.
40. I love violent sports and movies.
41. Sometimes you have to pretend you like people to get something out of them.
42. I am an impulsive person.
43. I have taken hard drugs (e.g., heroin, cocaine).
44. I'm a soft-hearted person.
45. I can talk people into anything.
46. I never shoplifted from a store.
47. I don□t enjoy taking risks.
48. People are too sensitive when I tell them the truth about themselves.
49. I was convicted of a serious crime.
50. Most people tell lies everyday.
51. I keep getting in trouble for the same things over and over.
52. Every now and then I carry a weapon (knife or gun) for protection.
53. People cry way too much at funerals.
54. You can get what you want by telling people what they want to hear.
55. I easily get bored.
56. I never feel guilty over hurting others.
57. I have threatened people into giving me money, clothes, or makeup.
58. A lot of people are “suckers” and can easily be fooled.
59. I admit that I often “mouth off” without thinking.
60. I sometimes dump friends that I don□t need any more.
61. I would never step on others to get what I want.
62. I have close friends who served time in prison.
63. I purposely tried to hit someone with the vehicle I was driving.
64. I have violated my parole from prison.

Buss-Perry Aggression Questionnaire (BPAQ)

AQ: For each statement, please circle a number to show how much the statement matches what you are like or what you think.	Not like like me at all		Sort of like me		A lot like me
1. When frustrated, I let my irritation show.	1	2	3	4	5
2. Given enough provocation, I may hit another person.	1	2	3	4	5
3. My friends say that I'm somewhat argumentative.	1	2	3	4	5
4. Some of my friends think I'm a hothead.	1	2	3	4	5
5. I often find myself disagreeing with people.	1	2	3	4	5
6. At times I feel I have gotten a raw deal out of life.	1	2	3	4	5
7. I can think of no good reason for ever hitting a person.	1	2	3	4	5
8. When people are especially nice, I wonder what they want.	1	2	3	4	5
9. If somebody hits me, I hit back.	1	2	3	4	5
10. I have become so mad that I have broken things.	1	2	3	4	5
11. I am suspicious of overly friendly strangers.	1	2	3	4	5
12. Once in a while I can't control the urge to strike another person.	1	2	3	4	5
13. I tell my friends openly when I disagree with them.	1	2	3	4	5
14. I sometimes feel that people are laughing at me behind my back.	1	2	3	4	5
15. If I have to resort to violence to protect my rights, I will.	1	2	3	4	5
16. I can't help getting into arguments when people disagree with me.	1	2	3	4	5
17 There are people who pushed me so far that we came to blows.	1	2	3	4	5
18. Other people always seem to get the breaks.	1	2	3	4	5
19. I am an even-tempered person.	1	2	3	4	5
20. I know that "friends" talk about me behind my back.	1	2	3	4	5
21. I have threatened people I know.	1	2	3	4	5
22. Sometimes I fly off the handle for no good reason.	1	2	3	4	5
23. When people annoy me, I may tell them what I think of them.	1	2	3	4	5
24. I get into fights a little more than the average person.	1	2	3	4	5
25. I have trouble controlling my temper.	1	2	3	4	5
26. I flare up quickly but get over it quickly.	1	2	3	4	5
27. I am sometimes eaten up with jealousy.	1	2	3	4	5
28. I wonder why sometimes I feel so bitter about things.	1	2	3	4	5
29. I sometimes feel like a powder keg ready to explode.	1	2	3	4	5

Buss-Perry, J. Pers. and Soc. Psychology, 1992, vol.63, No.3, 452-459.

Barratt Impulsivity Scale-11 (BIS-11)

PERSONAL EVALUATION - BIS 11

:_____ DATE:___/___/___

DIRECTIONS: This is a test to measure some of the ways you think and act. Read each statement, and circle either (1-rarely/never), (2-once in a while), (3-often), or (4-almost always/never). Circle only one number for each statement. Do not spend too much time on any statement. Answer quickly and honestly.

1 - Rarely/Never 2 - Once in a while 3 - Often 4 - Almost Always/Always

1.	I plan tasks carefully	1	2	3	4
2.	I do things without thinking	1	2	3	4
3.	I make up my mind quickly	1	2	3	4
4.	I am happy-go-lucky	1	2	3	4
5.	I don't "pay attention"	1	2	3	4
6.	I have "racing" thoughts	1	2	3	4
7.	I plan trips well ahead of time	1	2	3	4
8.	I am self-controlled	1	2	3	4
9.	I concentrate easily	1	2	3	4
10.	I save regularly	1	2	3	4
11.	I "squirm" at plays or lectures (speeches)	1	2	3	4
12.	I am a careful thinker	1	2	3	4
13.	I plan for job security	1	2	3	4
14.	I say things without thinking	1	2	3	4
15.	I like to think about complex (hard) problems	1	2	3	4
16.	I change jobs	1	2	3	4
17.	I act "on impulse"	1	2	3	4
18.	I get easily bored when solving thought problems	1	2	3	4
19.	I act on the spur of the moment	1	2	3	4
20.	I am a steady thinker	1	2	3	4
21.	I change residences (where I live)	1	2	3	4
22.	I buy things on impulse	1	2	3	4
23.	I can only think about one problem at a time	1	2	3	4
24.	I change hobbies	1	2	3	4
25.	I spend or charge more than I earn	1	2	3	4
26.	I have extraneous (outside) thoughts when thinking	1	2	3	4
27.	I am more interested in the present than the future	1	2	3	4
28.	I am restless at the theater or lectures	1	2	3	4
29.	I like puzzles	1	2	3	4
30.	I am future oriented	1	2	3	4

Impulsive-Premeditated Aggression Scale (IPAS)

I/APS

When people become frustrated, angry or enraged they express that anger in a variety of ways. Considering times when you have become aggressive and please answer the following questions. Aggressive actions are defined as hitting, pushing, or verbally insulting another person or breaking/throwing objects because you were angry or frustrated.

Your possible answers are:

Strongly Agree = **SA**, Agree = **A**, Neutral = **N**, Disagree = **D**, Strongly Disagree = **SD**

	SA	**A**	**N**	**D**	**SD**
1. I planned when and where my anger was expressed.	O	O	O	O	O
2. I felt my outbursts were justified.	O	O	O	O	O
3. When angry I reacted without thinking.	O	O	O	O	O
4. I typically felt guilty after the aggressive acts.	O	O	O	O	O
5. I was in control during the aggressive acts.	O	O	O	O	O
6. I feel my actions were necessary to get what I wanted.	O	O	O	O	O
7. I usually can't recall the details of the incidents well.	O	O	O	O	O
8. I understood the consequences of the acts before I acted.	O	O	O	O	O
9. I feel I lost control of my temper during the acts.	O	O	O	O	O
10. Sometimes I purposely delayed the acts until a later time.	O	O	O	O	O
11. I felt pressure from others to commit the acts.	O	O	O	O	O
12. I wanted some of the incidents to occur.	O	O	O	O	O
13. I feel some of the incidents went too far.	O	O	O	O	O
14. I think the other person deserved what happened to them during some of the incidents.	O	O	O	O	O
15. I became agitated or emotionally upset prior to the acts.	O	O	O	O	O
16. The acts led to power over others or improved social status for me.	O	O	O	O	O
17. I was under the influence of alcohol or other drugs during the acts.	O	O	O	O	O
18. I knew most of the persons involved in the incidents.	O	O	O	O	O
19. I was concerned for my personal safety during the acts.	O	O	O	O	O
20. Some of the acts were attempts at revenge.	O	O	O	O	O
21. I feel I acted out aggressively more than the average person over the last six months.	O	O	O	O	O
22. I was confused during the acts.	O	O	O	O	O
23. Prior to the incidents I knew an altercation was going to occur.	O	O	O	O	O
24. My behavior was too extreme for the level of provocation.	O	O	O	O	O
25. My aggressive outbursts were usually directed at a specific person.	O	O	O	O	O
26. I consider the acts to have been impulsive.	O	O	O	O	O
27. I was in a bad mood the day of the incident.	O	O	O	O	O
28. The acts were a "release" and I felt better afterwards.	O	O	O	O	O
29. I am glad some of the incidents occurred.	O	O	O	O	O
30. Anything could have set me off prior to the incidents.	O	O	O	O	O

A1.I Summary of POMS data (Δ Scores: Post-Dose minus Pre-Dose).
D = Depression-Dejection; V = Vigor; Confusion = Confusion-Bewilderment; TA = Tension Anxiety; AH = Anger-Hostility; F = Fatigue. Min_PostDose = minutes since dose (30, 60, 150, 210, refers to session 1, 2, 3, 4, respectively).
IU =international unit. Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	D	V	CB	TA	AH	F
30	-0.50 1.22	1.00 3.10	-0.17 0.41	-1.00 1.67	-0.33 0.82	-1.67 1.86
90	-1.17 2.04	0.00 2.90	0.00 0.00	-0.50 0.84	-0.33 0.82	-1.17 2.14
150	-1.17 2.04	-3.17 2.48	-0.17 0.41	-0.67 1.75	-0.50 0.84	-1.33 2.80
210	-0.60 1.95	-1.20 2.59	0.40 0.89	1.60 2.07	-0.40 1.52	0.40 3.51

OT Dose (12 IU)

Min_PostDose	D	V	CB	TA	AH	F
30	0.00 0.00	-0.33 1.86	0.00 0.00	-1.17 1.60	0.00 0.00	-0.67 1.51
90	0.17 0.41	0.00 0.89	0.00 0.00	-1.00 1.55	0.00 0.00	-0.17 2.32
150	0.33 0.82	-0.83 2.14	0.00 0.00	0.17 1.47	0.00 0.00	0.50 2.95
210	0.40 0.89	-2.00 3.16	0.00 0.00	0.60 1.34	0.40 0.89	1.60 4.22

OT Dose (24 IU)

Min_PostDose	D	V	CB	TA	AH	F
30	-0.33 0.52	-1.50 1.76	0.00 0.00	0.00 1.26	0.00 0.00	0.00 0.63
90	-0.33 0.52	-0.17 1.94	0.00 0.00	-0.67 1.21	0.00 0.00	-1.00 2.00
150	-0.50 0.84	-1.00 2.19	0.33 0.82	-0.17 1.60	0.00 0.00	0.17 3.43
210	-0.20 0.45	-2.40 1.67	0.00 0.00	-0.80 1.30	0.00 0.00	1.20 1.10

OT Dose (48 IU)

Min_PostDose	D	V	CB	TA	AH	F
30	0.17 0.41	0.83 0.98	0.00 0.00	-0.67 1.03	0.00 0.00	-0.50 0.55
90	0.00 0.00	1.33 1.97	0.00 0.00	-0.50 0.84	0.67 1.63	0.00 1.55
150	0.33 0.82	0.33 1.86	0.00 0.00	-0.17 0.98	0.00 0.00	0.17 1.72
210	0.00 0.00	-0.80 0.84	0.00 0.00	0.00 1.22	0.00 0.00	2.00 3.94

A1.I Summary of POMS raw data

D = Depression-Dejection; V = Vigor; Confusion = Confusion-Bewilderment; TA = Tension Anxiety; AH = Anger-Hostility; F = Fatigue. Min_PostDose = minutes since dose (-30 refers to the pre-dose values. 30, 60, 150, 210, refers to Post-Dose session 1, 2, 3, 4, respectively). IU =international unit.
Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	D	V	CB	TA	AH	F
-30	2.50 4.46	12.83 6.71	0.50 1.22	1.33 2.07	0.83 1.33	3.50 2.88
30	2.00 3.35	13.83 6.21	0.33 0.82	0.33 0.82	0.50 1.22	1.83 1.47
90	1.33 2.42	12.83 6.94	0.50 1.22	0.83 1.33	0.50 1.22	2.33 2.16
150	1.33 2.42	9.67 8.69	0.33 0.82	0.67 1.21	0.33 0.82	2.17 2.32
210	0.20 0.45	10.60 5.77	0.40 0.89	2.40 2.88	0.20 0.45	4.00 3.54

OT Dose (12 IU)

Min_PostDose	D	V	CB	TA	AH	F
-30	1.17 2.86	12.17 6.85	0.33 0.82	1.50 1.87	0.00 0.00	2.17 2.14
30	1.17 2.86	11.83 7.47	0.33 0.82	0.33 0.52	0.00 0.00	1.50 1.22
90	1.33 3.27	12.17 7.22	0.33 0.82	0.50 0.84	0.00 0.00	2.00 1.79
150	1.50 3.67	11.33 8.09	0.33 0.82	1.67 2.25	0.00 0.00	2.67 2.66
210	0.40 0.89	9.20 6.91	0.00 0.00	1.40 1.95	0.40 0.89	4.00 3.81

OT Dose (24 IU)

Min_PostDose	D	V	CB	TA	AH	F
-30	1.33 2.80	14.00 5.80	0.33 0.82	0.67 1.21	0.00 0.00	2.83 3.92
30	1.00 2.45	12.50 6.92	0.33 0.82	0.67 1.21	0.00 0.00	2.83 4.02
90	1.00 2.45	13.83 6.05	0.33 0.82	0.00 0.00	0.00 0.00	1.83 2.23
150	0.83 2.04	13.00 6.63	0.67 1.63	0.50 1.22	0.00 0.00	3.00 3.41
210	0.00 0.00	10.80 7.56	0.00 0.00	0.00 0.00	0.00 0.00	4.00 4.24

OT Dose (48 IU)

Min_PostDose	D	V	CB	TA	AH	F
-30	0.83 2.04	12.50 6.22	0.33 0.82	0.83 0.98	0.00 0.00	1.33 1.51
30	1.00 2.45	13.00 6.13	0.33 0.82	0.17 0.41	0.00 0.00	0.83 0.98
90	0.83 2.04	13.50 6.09	0.33 0.82	0.33 0.52	0.67 1.63	1.33 1.21
150	1.17 2.86	12.50 7.15	0.33 0.82	0.67 1.03	0.00 0.00	1.50 1.05
210	0.00 0.00	11.60 7.13	0.00 0.00	1.00 1.41	0.00 0.00	3.00 5.10

A1.J Informed consent document

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER - HOUSTON

Oxytonin Effects on Computer-Based Social Interaction
HSC-MS 12-0024

INFORMED CONSENT FORM TO TAKE PART IN RESEARCH

INVITATION TO TAKE PART

You are invited to take part in a research project called, "Oxytonin Effects on Computer-Based Social Interaction," conducted by Joseph L. Alcorn III and Dr. Scott Lane of the University of Texas Health Science Center Houston. For this research project, Joseph L. Alcorn III will be called the Principal Investigator.

Your decision to take part is voluntary and you may refuse to take part, or choose to stop taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from your doctor, or the University of Texas Health Science Center.

This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-10-0178.

DESCRIPTION OF RESEARCH

PURPOSE

The purpose of this research is to examine how the drug, Syntocinon (synthetic oxytocin), affects people's mood (e.g. anger, frustration, cooperativeness), and the way that people interact with each other during a computer task. This is a Food and Drug Administration (FDA) approved drug that has been shown in other studies to affect mood, personality, and emotional responses on the spectrum of behavior. This is a local study in Houston, Texas. The study will enroll a total of 50 people. The National Institute of Health is paying for this study to be completed.

PROCEDURES

Before you can be enrolled in this study we made sure that you meet certain criteria. To ascertain this, we asked you to complete a physical exam, a mental health exam, and answer questions about drug use and medical history. You have met our health requirements, now we will ask if you wish to proceed to participate in this study. This study will last five days. On the first day you will not receive a drug or placebo dose. On the remaining four experimental days, you will be given a nasal spray containing either a dose of the drug Syntocinon or a placebo (nasal spray containing no Syntocinon). You will be asked to inhale a total volume of 1.5ml in both nostrils (at an approximate volume of 0.75 ml in each nostril) on days 2-5. Over the course of this study you

will receive both the study drug and the placebo, however, you will not know if you are taking the drug or the placebo at the time that you are taking the drug. After taking the nasal spray, you will work on a task where you will interact with other people through a computer. Below is an outline of the study days:

Outline of Study Days
Day 1: Introduction to the computer task: no dose
Day 2: Computer task: Syntocinon dose or placebo
Day 3: Computer task: Syntocinon dose or placebo
Day 4: Computer task: Syntocinon dose or placebo
Day 5: Computer task: Syntocinon dose or placebo

Each day you will also be asked to provided a breath sample to test for recent alcohol use. The results of these tests will determine if you can take part in the study on that day. At 8:30am you will be given either the study medication, called Syntocinon or a placebo (a nasal spray not containing Syntocinon). During testing you will be in a room with a computer monitor screen and a response panel with three buttons. The task will require that you push the buttons to earn money. You will be paired with other people through the computer during the test session. Completing the task may cause you to react and may present a challenge to youThe way you interact with these other people may affect the amount of money you earn. The sessions will be about 25 minutes each, and there will be a break in between test sessions. After each session you will be asked questions about your mood and then your heart rate and blood pressure will be measured and collected. At the end of each day, you will be paid the sum money earned during each session. At the request of the FDA under the Division of Psychiatry Products (DPP) you will be asked questions pertaining to suicidal thought and behaviors. This is a recent policy of the DPP to monitor treatment-emergent suicidality and to ensure that volunteers in clinical research who are experiencing suicidality are detected and adequately managed. Below is a typical daily schedule during the study.

Daily Schedule
8:00 am: Urine and expired breath sample collection.
8:30 am: mood questionaires; heart rate/blood pressure; Placebo/dose administration (days 2-5)
9:00 am: Session #1 of computer task; mood questionaires; heart rate/blood pressure.
10:00 am: Session #2 of computer task; mood questionaires; heart rate/blood pressure.
11:00 am: Session #3 of computer task; mood questionaires; heart rate/blood pressure.
12:00 pm: Session #4 of computer task; mood questionaires; heart rate/blood pressure.
12:30 pm: Lunch
1:00 pm: Impairment evaluation and questionnaires
1:15 pm: Payment and release from laboratory.

You are asked to not use alcohol or any other drug during the entire study. You are asked not to drink tea, coffee, or colas, smoke cigarettes, or eat food from outside during the test days. These requirements are very important to the study. Every day you visit the medical center, you will be asked to provide a urine sample to test for recent drug use. You may refuse to answer any questions asked or written on any forms.

TIME COMMITMENT
You will be asked to come into the laboratory for 5 days, approximately 5-6 hours each day. Your total time in the study should be about 1 week.

BENEFITS:
You may receive no direct benefit from participating in this study. However, you may learn new information regarding your physical and mental health status obtained during the screening procedures. You will be provided a referral service if one is available that might benefit you.

RISKS AND DISCOMFORTS
Taking part in this study involves the following risks:

Syntocinon is a synthetic oxytocin approved by the FDA for the treatment for conditions, such as uterine haemorrhage and augmentation of labor. A single dose of Syntocinon is not expected to cause any serious changes to your health. The most common side effects of Syntocinon reported by the manufacturer compared to placebo are lighthededness/headache, dry mouth, nasal irritation, and drowsiness. Syntocinon should not be taken if you have a serve cardiovascular disorder or if you are allergic to oxytocin or preservatives (i.e. sodium acetate, glacial acetic acid, chlorbutol, and ethanol 94%). Due to this fact you will not be able to take part in this study in you have a history of allergic reactions to oxytocin or preservatives, or if you have diabetes, chronic high blood pressure, glaucoma, or a cardiac disorder (e.g. arrhythmia). Risks may include the possible breach of confidentiality.

ALTERNATIVES:
The only alternative is not to take part in this study.

STUDY WITHDRAWAL:
You may withdraw at any time without any penalty or unfair outcomes should you choose to stop taking part in this study. You may be asked to leave the study for the following reasons:
1. If alcohol is detected on your breath and/or drugs are found in your urine sample.
2. You fail to show up for three scheduled appointments at the laboratory, and do not contact the laboratory.
3. You experience side effects of Syntocinon that are considered to be unsafe for you to continue.

IN CASE OF INJURY
If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Scott Lane at (713) 486-2535 and to the Committee for the Protection of Human Subjects at (713) 500-7943. You will not give up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT, AND COMPENSATION

Parking voucher or bus tokens and lunch will be provided. You can expect to earn about $8-10 per hour.

It will not cost you anything to join this study. If you should receive a bill that you believe is related to your taking part in this research project, please contact, the Principal Investigator, Joseph L. Alcorn III at (713) 486-2613.

You wll be paid for taking part in this project in the following amounts:

1. On experimental days, you will earn about $5-7 per testing session, based on your performance.
2. You will earn $20 each day that you arrive on time for scheduled appointment and your breath alcohol level and urine sample are free from drugs and alcohol.
3. Upon completion of the experiment (on the last day), you will earn a completion bonus of $10 for each day that you took part (e.g., 5 days = $50).
4. You will receive $8/hour for your time today, for the physical examination, and for the final day when you fill out questionnaires. There is the possibility, but no guarantee, of earning up to $138 on the last day of study participation.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration, National Institute of Health (NIH) and the Committee for the Protection of Human Subjects may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. There is a separate authorization form that you will be asked to sign which details the use and disclosure of your protected health information.

QUESTIONS:

The Principal Investigator, Joseph L. Alcorn III and his research staff will be glad to answer any questions regarding the study at any time. The staff may be reached at (713) 486-2794.

SIGNATURES:

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research s**ub**ject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

_____

Printed Name of Subject

_____ _____

Signature of Subject Date / Time

_____

Printed Name of Individual Obtaining Consent

_____ _____

Signature of Individual Obtaining Consent Date / Time

CPHS STATEMENT: This study (HSC-XX-XX-XXXX) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the Univeristy of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

A1.K Point Subtraction Aggression Paradigm (PSAP) Instructions

This computer task examines mood, motor responses (button pressing), and interaction with other people. Each session will last approximately25 minutes. During the session you will be able to earn money by working at a response panel. This is a drawing of the response panel. As the drawing shows, the response panel has three buttons marked A, B, and C; a monitor, which will display the letters A, B, and C; and a money counter. When you press a button,

the letter corresponding to that button will remain on the screen and the other letters will go off the screen. So when you press the A button, the letters B and C will disappear. Pressing button B removes the letters A and C, and pressing button C removes letters A and B. When one only one letter is showing on the screen, the other buttons will not work. So, you can only change from one button to another button when all three letters are displayed on the screen. Your response panel is linked by a network to one of several other panels just like it. Other people like you will be seated at the same kind of panel. The panels are located in different locations. The other person will always be a (man/woman), as we pair people by the same gender in this task. When the session starts, the letters A, B, and C will be displayed and the money counter will begin at zero. If you press button A, letters B and C letter will disappear. Pressing button A approximately 100 times will add 15 cents to your counter (you don't need to count presses, the computer program will do it for you). Then the A, B, and C letters will come back on the screen, and you can continue to press button A or switch to buttons B or C. During the session, you may see the counter increase in size and start flashing off and on. Then 15 cents will then be subtracted from your counter, and the counter will return to its normal size. This means that the other person – whose computer in linked to yours – has subtracted 15 cents from your counter and added it to his counter by pressing button B on his response panel 10 times. So the other person can take 15 cents of your money and add it to his money by pressing B ten times, instead of pressing A 100 times.

If YOU press button B, the A and C letters will disappear. Then pressing button B ten times will subtract 15 cents from the counter of the person who is connected to your panel. When the A, B, and C letters reappear, you can continue to press button B or switch to button A or C. However, if you subtract money from the other person, it will not be added to your counter – the money is just removed from the other person's counter. There are two conditions in the task. In condition 1, the person keeps the money that s/he subtracts. In condition 2, the money that is taken from the other person is simply gone. The conditions are determined randomly by the toss of a coin and you ended up in the condition 2 in which you do not keep the money you subtract. If you press button C, the A and B letters will disappear. Pressing button C until the letter C goes off the screen (approximately 10 times) will protect your counter from subtractions for a short period of time (about 2 minutes). When the A, B, and C letters reappear, you may continue to press button C or switch to button A or B. You will be paid the money showing on your counter at the end of each test session. This money will be paid at the end of the day, after you have completed your last session. How much you earn depends mostly on how fast you press the A button. As a general rule, the faster you press button A the more money you can earn. Please remain in the testing room until you see a message on the computer screen that reads “Session Over”.

APPENDIX MATERIAL FOR EXPERIMENT 2 (CHAPTER 3)

A2.A Summary of behavioral data (raw data)

ButtonA = Monetary Response Rate (responses per second); ButtonB1 = Aggressive Response Rate (responses per minute) with the outlier; ButtonB2 = Aggressive Response Rate (responses per minute) without the outlier. Min_PostDose = minutes since dose (-30 refers to the Pre-Dose session. 30, 60, 150, refers to Post-Dose sessions 1, 2, 3, respectively). IU =international unit. Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	ButtonA	ButtonB1	ButtonB2
-30	4.62 0.72	7.83 4.74	7.83 4.74
30	4.61 0.74	7.52 4.66	7.52 4.66
90	4.58 0.83	7.66 6.49	7.66 6.49
150	7.16 10.24	9.11 6.07	8.23 5.05

OT Dose (24 IU)

Min_PostDose	ButtonA	ButtonB1	ButtonB2
-30	4.59 0.58	7.66 3.15	7.66 3.15
30	4.59 0.60	6.98 2.68	6.98 2.68
90	4.58 0.69	7.65 3.40	7.65 3.40
150	4.71 0.71	7.49 4.38	7.49 4.38

A2.B Summary of psychometric data (raw data)

IM = interpersonal manipulation subscale; CA = callous affect subscale; ELS = erratic lifestyle subscale; CT = criminal tendencies; SRPIII = total score of the self-report of psychopathy III. Anger = anger subscale; Host = hostility subscale; Physical = physical aggression subscale; Verbal = verbal aggression subscale.

Self-Report of Psychopathy III

stats	IM	CA	ELS	CT	SRPIII
mean	35.76	40.76	37.59	26.94	140.71
sd	7.39	7.27	6.25	7.20	21.66

Buss-Perry Aggression Questionnaire

stats	Anger	Host	Physical	Verbal	BPAQ
mean	11.00	14.6471	18.59	11.88	56.12
sd	3.00	4.30031	5.04	2.78	11.74

A2.C Summary of "Likability" ratings (raw data)
VAS1 = Social Visual Analog Scale, Likability ratings with the outlier. VAS2 = Social Visual Analog Scale, Likability ratings without the outlier. Min_PostDose = minutes since dose (-30 refers to the Pre-Dose session. 30, 60, 150, refers to Post-Dose sessions 1, 2, 3, respectively). IU =international unit.Top number represents the mean. Bottom number represents the S.D.

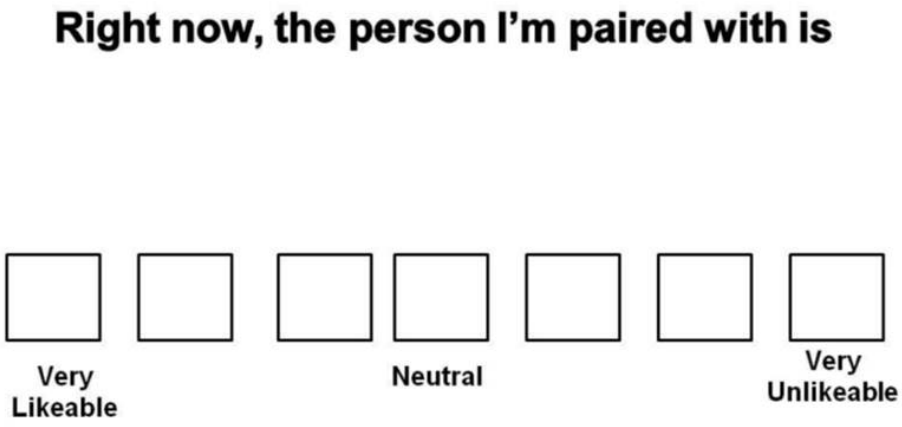
Placebo Dose

Min_PostDose	VAS1	VAS2
-30	3.44 1.77	3.44 1.77
30	3.00 1.97	3.00 1.97
90	3.21 1.99	3.21 1.99
150	2.62 2.20	2.80 2.17

OT Dose (24 IU)

Min_PostDose	VAS1	VAS2
-30	2.82 2.04	2.82 2.04
30	2.88 2.18	2.88 2.18
90	2.47 1.81	2.47 1.81
150	2.41 2.00	2.41 2.00

Social Visual Analog Scale (VAS)



A2.D Summary of cardiovascular data (raw data)

HR1 = Heart Rate (beats per minute) with the outlier; HR2 = Heart Rate (beats per minute) without the outlier; SBP = Systolic Blood Pressure (mmHG); DBP1 = Systolic Blood Pressure (mmHG) with the outlier; DBP2 = Systolic Blood Pressure (mmHG) without the outlier. Min_PostDose = minutes since dose (-30 refers to the Pre-Dose session. 30, 60, 150, refers to Post-Dose sessions 1, 2, 3, respectively). IU =international unit.Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	HR	HR2	SBP	DBP	DBP2
-30	69.63 11.74	69.63 11.74	110.63 9.82	69.31 10.46	69.31 10.46
30	66.88 13.63	65.53 12.97	114.56 11.40	73.44 9.04	73.44 9.04
90	64.56 11.39	64.56 11.39	116.19 9.83	74.88 10.31	74.60 10.61
150	63.56 11.86	63.56 11.86	114.19 9.57	73.75 8.43	73.75 8.43

OT Dose (24 IU)

Min_PostDose	HR	HR2	SBP	DBP	DBP2
-30	69.59 11.69	69.59 11.69	111.00 9.39	70.65 11.20	70.65 11.20
30	66.65 13.12	66.65 13.12	110.71 9.92	70.88 11.25	70.88 11.25
90	65.41 13.61	65.41 13.61	113.24 10.13	71.71 10.20	71.71 10.20
150	65.00 12.60	65.00 12.60	114.18 9.47	73.41 8.83	73.41 8.83

A2.E Summary of temperature data (raw data)

Temp = Oral body temperature (Fº). Min_PostDose = minutes since dose (-30 refers to the Pre-Dose session. 30, 60, 150, refers to Post-Dose sessions 1, 2, 3, respectively). IU =international unit.Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	Temp
-30	97.29 0.92
30	97.14 0.78
90	97.36 0.79
150	97.27 0.89

OT Dose (24 IU)

Min_PostDose	Temp
-30	97.49 0.80
30	97.05 0.89
90	97.42 0.70
150	97.15 0.70

A2.F Summary of POMS data (Δ Scores: Post-Dose minus Pre-Dose).

D = Depression-Dejection; V = Vigor; Confusion = Confusion-Bewilderment; TA1 = Tension Anxiety with the outlier; TA2 = Tension Anxiety without the outlier; AH = Anger-Hostility; F = Fatigue. Min_PostDose = minutes since dose. 30, 60, 150, refers to Post-Dose sessions 1, 2, 3, respectively). IU =international unit.Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	D	V	CB	TA1	TA2	AH	F
30	-0.06 0.24	0.56 2.12	0.00 0.00	0.25 0.43	0.25 0.43	0.00 0.00	0.68 1.49
90	0.00 0.35	-0.25 3.07	0.19 0.39	-0.06 0.56	-0.06 0.56	0.25 0.66	0.75 1.20
150	0.06 0.56	-0.62 3.04	0.31 0.68	0.13 0.93	0.13 0.96	0.31 0.85	1.19 1.74

OT Dose (24 IU)

Min_PostDose	D	V	CB	TA1	TA2	AH	F
30	-0.18 0.39	0.94 2.19	-0.12 0.33	0.00 0.61	0.00 0.61	-0.18 0.53	-0.65 1.37
90	-0.18 0.53	0.88 2.29	-0.12 0.33	0.65 1.90	0.25 1.00	-0.06 0.75	-0.76 2.08
150	-0.24 0.56	1.24 5.12	0.00 0.50	-0.06 0.83	-0.06 0.83	0.06 1.14	-0.47 1.50

A2.G Summary of POMS (raw data)

D = Depression-Dejection; V = Vigor; Confusion = Confusion-Bewilderment; TA1 = Tension Anxiety with the outlier; TA2 = Tension Anxiety without the outlier; AH = Anger-Hostility; F = Fatigue. Min_PostDose = minutes since dose (-30 refers to the Pre-Dose session. 30, 60, 150, refers to Post-Dose sessions 1, 2, 3, respectively). IU =international unit.Top number represents the mean. Bottom number represents the S.D.

Placebo Dose

Min_PostDose	D	V	CB	TA1	TA2	AH	F
-30	0.06 0.24	12.06 7.37	0.22 0.43	0.94 1.21	0.94 1.21	0.06 0.24	0.39 0.70
30	0.00 0.00	12.56 6.99	0.22 0.43	1.22 1.31	1.22 1.31	0.06 0.24	1.00 1.75
90	0.11 0.32	11.67 7.18	0.44 0.78	0.78 1.17	0.78 1.17	0.39 0.78	1.06 1.35
150	0.22 0.65	11.44 7.89	0.56 0.98	1.00 1.19	1.00 1.19	0.44 0.92	1.44 2.09

OT Dose (24 IU)

Min_PostDose	D	V	CB	TA1	TA2	AH	F
-30	0.33 0.69	10.72 7.76	0.22 0.55	0.78 1.11	0.78 1.11	0.17 0.51	1.22 2.21
30	0.11 0.32	11.61 7.04	0.11 0.47	0.78 1.11	0.78 1.11	0.00 0.00	0.67 1.14
90	0.06 0.24	11.56 7.39	0.11 0.32	1.39 2.25	0.94 1.25	0.11 0.47	0.56 0.86
150	0.00 0.00	11.89 6.78	0.22 0.43	0.78 1.17	0.78 1.17	0.22 0.94	0.89 1.32

A2.H Informed Consent Document

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER - HOUSTON

Oxytonin Effects on Computer-Based Social Interaction
HSC-MS-12-0024

INFORMED CONSENT FORM TO TAKE PART IN RESEARCH

INVITATION TO TAKE PART

You are invited to take part in a research project called, "Oxytonin Effects on Computer-Based Social Interaction," conducted by Joseph L. Alcorn III and Dr. Scott Lane of the University of Texas Health Science Center Houston. For this research project, Joseph L. Alcorn III will be called the Principal Investigator.

Your decision to take part is voluntary and you may refuse to take part, or choose to stop taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from your doctor, or the University of Texas Health Science Center.

This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-10-0178.

DESCRIPTION OF RESEARCH

PURPOSE

The purpose of this research is to examine how the drug, Syntocinon (synthetic oxytocin), affects people's mood (e.g. anger, frustration, cooperativeness), and the way that people interact with each other during a computer task. This is a Food and Drug Administration (FDA) approved drug that has been shown in other studies to affect mood, personality, and emotional responses on the spectrum of behavior. This is a local study in Houston, Texas. The study will enroll a total of 50 people. The National Institute of Health is paying for this study to be completed.

PROCEDURES

Before you can be enrolled in this study we made sure that you meet certain criteria. To ascertain this, we asked you to complete a physical exam, a mental health exam, and answer questions about drug use and medical history. You have met our health requirements, now we will ask if you wish to proceed to participate in this study. This study will last an expected five days (see Time Commitment section below for details). On the first day you will not receive a drug or placebo dose. On two of the remaining experimental days, you will be given a nasal spray containing either a dose of the drug Syntocinon or a placebo (nasal spray containing no Syntocinon). You will be asked to inhale a total volume of 1.5ml (≈ 0.3 tsp) in both nostrils (at an approximate volume of 0.75 ml (≈ 0.15 tsp) in each nostril). On other days, you may simply

participate in the computer tasks, and will not receive any nasal spray. Over the course of this study you will receive both the study drug and the placebo, however, you will not know if you are taking the drug or the placebo at the time that you are taking the drug. After taking the nasal spray, you will work on a task where you will interact with other people through a computer. Below is an outline of the study days:

Outline of expected study Days

Step 1: Introduction to the computer task: No dose (may last more than 1 day)
Step 2: Computer task: Syntocinon dose or placebo
Step 3: Computer task: No dose (may last more than 1 day)
Step 4: Computer task: Syntocinon dose or placebo

Each day you will also be asked to provided a breath sample to test for recent alcohol use. The results of these tests will determine if you can take part in the study on that day. At 8:30am you will be given either the study medication, called Syntocinon or a placebo (a nasal spray not containing Syntocinon). During testing you will be in a room with a computer monitor screen and a response panel with three buttons. The task will require that you push the buttons to earn money. You will be paired with other people through the computer during the test session. Completing the task may cause you to react and may present a challenge to you. The way you interact with these other people may affect the amount of money you earn. The sessions will be about 25 minutes each, and there will be a break in between test sessions. After each session you will be asked questions about your mood and then your heart rate and blood pressure will be measured and collected. At the end of each day, you will be paid the sum money earned during each session. At the request of the FDA under the Division of Psychiatry Products (DPP) you will be asked questions pertaining to suicidal thought and behaviors. This is a recent policy of the DPP to monitor treatment-emergent suicidality and to ensure that volunteers in clinical research who are experiencing suicidality are detected and adequately managed. Below is a typical daily schedule during the study.

Expected daily Schedule

8:00 am Urine and expired breath sample collection.
8:30 am: Session #1 of computer task; mood questionaires; heart rate/blood pressure; temperature.
9:00 am: Placebo/ Syntocinon dose administration (on scheduled days)
9:30 am: Session #2 of computer task; mood questionaires; heart rate/blood pressure; temperature.
10:30 am: Session #3 of computer task; mood questionaires; heart rate/blood pressure; temperature.
11:30 am: Session #4 of computer task; mood questionaires; heart rate/blood pressure; temperature.
12:00 pm: Lunch
12:30 pm: Impairment evaluation and questionnaires
12:45 pm: Payment and release from laboratory.

You are asked to not use other drugs during the entire study. On testing days, you are asked not to drink tea, coffee, or colas, smoke cigarettes, or eat food from outside before or during your participation (after you leave the laboratory these items are OK). These requirements are very important to the study. Every day you visit the medical center, you will be asked to provide a urine sample to test for recent drug use. You may refuse to answer any questions asked or written on any forms.

TIME COMMITMENT

You will be asked to come into the laboratory for an expected 5 days, approximately 5.5-6 hours each day. Your total time in the study should be about 1 week. However, due to the fact that the we must synch up your behavioral data from the computer task with the behavioral data of the person who you are paired with missing data might occur. Therefore, we might sometimes ask you to repeat an experimental day. You will still be compensated as described in the costs, reimburstments, and compensations section below. As, such your participation in this study could take up to 20 days.

BENEFITS:

You may receive no direct benefit from participating in this study. However, you may learn new information regarding your physical and mental health status obtained during the screening procedures. You will be provided a referral service if one is available that might benefit you.

RISKS AND DISCOMFORTS

Taking part in this study involves the following risks:

Syntocinon is a synthetic oxytocin approved by the FDA for the treatment for conditions, such as uterine hemorrhage and augmentation of labor. A single dose of Syntocinon is not expected to cause any serious changes to your health. The most common side effects of Syntocinon reported by the manufacturer compared to placebo are lighthededness/headache, dry mouth, nasal irritation, and drowsiness. Syntocinon should not be taken if you have a serve cardiovascular disorder or if you are allergic to oxytocin or preservatives (i.e. sodium acetate, glacial acetic acid, chlorbutol, and ethanol 94%). Due to this fact you will not be able to take part in this study in you have a history of allergic reactions to oxytocin or preservatives, or if you have diabetes, chronic high blood pressure, glaucoma, or a cardiac disorder (e.g. arrhythmia). Risks may include the possible breach of confidentiality.

ALTERNATIVES:

The only alternative is not to take part in this study.

STUDY WITHDRAWAL:

You may withdraw at any time without any penalty or unfair outcomes should you choose to stop taking part in this study. You may be asked to leave the study for the following reasons:

4. If alcohol is detected on your breath and/or drugs are found in your urine sample.
5. You fail to show up for three scheduled appointments at the laboratory, and do not contact the laboratory.
6. You experience side effects of Syntocinon that are considered to be unsafe for you to continue.

IN CASE OF INJURY

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Scott Lane at (713) 486-2535 and to the Committee for the Protection of Human Subjects at (713) 500-7943. You will not give up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT, AND COMPENSATION

Parking voucher or bus tokens and lunch will be provided. You can expect to earn about $8-10 per hour.

It will not cost you anything to join this study. If you should receive a bill that you believe is related to your taking part in this research project, please contact, the Principal Investigator, Joseph L. Alcorn III at (713) 486-2613.

You wll be paid for taking part in this project in the following amounts:

5. On experimental days, you will earn about $5-7 per testing session, based on your performance.
6. You will earn $20 each day that you arrive on time for scheduled appointment and your breath alcohol level and urine sample are free from drugs and alcohol.
7. Upon completion of the experiment (on the last day), you will earn a completion bonus of $10 for each day that you took part (e.g., 4 days = $40).
8. You will receive $8/hour for your time today, for the physical examination, and for the final day when you fill out questionnaires. There is the possibility, but no guarantee, of earning up to $138 on the last day of study participation.

If you receive payment for taking part in this study please be informed that you will be asked to complete a copy W-9 form that will be forwarded to the accounting department as a requirement by the Internal Revenue Service. You will also be issued a 1099-Misc form from this study for tax reporting purposes. If you receive a bill that you believe is related to your taking part in this research study, please contact Joseph Alcorn III or research staff at at (713) 486-2794 with any questions.

CONFIDENTIALITY

Please understand that representatives of the Food and Drug Administration, National Institute of Health (NIH) and the Committee for the Protection of Human Subjects may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. There is a separate authorization form that you will be asked to sign which details the use and disclosure of your protected health information.

QUESTIONS:

The Principal Investigator, Joseph L. Alcorn III and his research staff will be glad to answer any questions regarding the study at any time. The staff may be reached at (713) 486-2794.

SIGNATURES:

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

_____

Printed Name of Subject

_____ _____

Signature of Subject Date / Time

_____

Printed Name of Individual Obtaining Consent

_____ _____

Signature of Individual Obtaining Consent Date / Time

CPHS STATEMENT: This study (HSC-MS-12-0024) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the Univeristy of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

BIBLIOGRAPHY

Ahern, T.H. & Young, L.J. (2009) The impact of early life family structure on adult social attachment, alloparental behavior, and the neuropeptide systems regulating affiliate behaviors in the monogamous prairie vole (microtus ochrogaster). Front Behav Neurosci. 3; 17.

Albein-Urios, N., Verdejo-Román, J., Soriano-Mas, C., Asensio, S., Martínez-González, J.M., & Verdejo-García, A. (2013) Cocaine users with comorbid Cluster B personality disorders show dysfunctional brain activation and connectivity in the emotional regulation networks during negative emotion maintenance and reappraisal. Eur Neuropsychopharmacol. Dec;23(12):1698-707

Alcorn III, J.L., Gowin, J.L., Green, C.E., Swann, A.C., Moeller, F.G., & Lane, S.D. (2013) Aggression, impulsivity, and psychopathic traits in combined antisocial personality disorder and substance use disorder. J Neuropsychiatry Clin Neurosci. Summer; 25 (3): 229-232.

Alcorn III, J.L., Rathnayaka, N., Swann, A.C, Moeller, F.G., & Lane, S.D. (In Press) Intranasal Oxytocin on Aggressive Responding in Antisocial Personality Disorder. The Psychol Rec

Alia-Klein, N., Goldstein, R.Z., Tomasi, D., Woicik, P.A., Moeller, S.J., Williams, B., Craig, I.W., Telang, F., Biegon, A., Wang, G.J., Fowler, J.S. & Volkow, N.D. (2009) Neural mechanisms of anger regulation as a function of genetic risk for violence. Emotion. Jun;9(3):385-96.

Allen, T.J., Moeller, F.G., Rhoades, H.M., & Cherek, D.R. (1997) Subjects with a history of drug dependence are more aggressive than subjects with no drug use history. Drug Alcohol Depend. 6, 46(1-2), 95-103.

Alterman, A.I. & Cacciola, J.S. (1991) The antisocial personality disorder diagnosis in substance abusers: problems and issues. J Nerv Mental Dis, 1797 (1991), pp. 401–409

Alterman, A.I., Cacciola, J.S., & Rutherford, M.J. (1993) Reliability of the Revised Psychopathy Checklist in substance abuse patients. Psychol Assess, 54, pp. 442–448

Alterman, A.I., McDermott, P.A., Cacciola, P.A., Rutherford, M.J. Boardman, M.J. McKay, J.R. & Cook, T.G. (1998) A typology of antisociality in methadone patients. J Abnorm Psychol, 1073 , pp. 412–422.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: Author

Anderson, D.A. (1999) The aggregate burden of crime. J. Law Econ. Vol 42, No. 2, 611-642.

Anderson, C.A. & Bushman, B.J. (2002) Human aggression. Annu Rev Psychol. 53: 27-51.

Anderson, N.E. & Kiehl, K.A. (2012) The psychopath magnetized: insights from brain imaging. Trends Cogn Sci. Jan;16(1):52-60.

Archer, J. (2004) Testosterone and human aggression: an evaluation of the challenge hypothesis. Neurosci Biobehav Rev. 30: 319–345

Arseneault, L., Moffitt, T.E., Caspi, A., Taylor, P.J., & Silva, P.A. (2000) Mental disorders and violence in a birth cohort: results from the Dunedin Study. Arch Gen Psychiatry. 57: 979-986.

Anderson, C.A. & Bushman, B.J. (2002) Human aggression. Annu Rev Psychol. 53: 27-51.

Averbeck, B.B., Bobin, T., Evans, S., & Shergill, S.S. (2012) Emotion recognition and oxytocin in patients with schizophrenia. Psychol Med. 2012 Feb;42(2):259-66.

Bakermans-Kranenburg, M.J., & van IJzendoorn, M.H. (2013) Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. Trans Psychiatry. 3, e258,

Baron, R.A. & Richardson, D.R. (1994) Human aggression. Plenum Press,New York.

Bartz, J., Simeon, D., Hamilton, H., Kim, S., Crystal, S., Braun, A., Vicen, V., & Hollander, E. (2010) Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci. Oct; 6(5): 556-563.

Bartz, J.A., Zaki, J., Bolger, N., & Ochsner, K.N. (2011) Social effects oxytocin in humans: context and person matter. Trend Cog Sci. Jul; 15(7): 301-309. 301-9.

Baumgartner, T., Heinrichs, M. Vonlanthen, A., Fischbacher, U., & Fehr, E. (2008) Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron. May 22; 58 (4): 639- 650.

Bethlehem, R.A., van Honk, J., Auyeung, B., & Baron-Cohen, S. Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies. Psychoneuroendocrinology. 2013 Jul;38(7):962-74

Benjamini, Y. & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. Annal of Stat, 29, 1165-1188.

Bjork, J.M., Doughtery, D.M., Moeller, F.G., Cherek, D.R., & Swann, A.C. (1999) The effects of tryptophan depletion and loading on laboratory aggression in men: time course and a food-restricted control. Psychopharmacology. Feb; 142(1): 24-30.

Bjork, J.M., Doughtery, D.M., Moeller, F.G., & Swann, A.C (2000) Differential behavioral effects of plasma tryptophan depletion and loading in aggressive and nonaggressive men. Neuropsychopharmacology. Apr;22(4):357-69.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., & Fehm, H.L. (2002) Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci. Jun; 5(6): 514-516.

Boccardi, M., Frisoni, G.B., Hare, R.D., Cavedo, E., Najt, P., Pievani, M., Rasser, P.E., Laakso, M.P., Aronen, H.J., Repo-Tiihonen, E., Vaurio, O., Thompson, P.M., Tiihonen, J. (2011) Cortex and amygdala morphology in psychopathy. Psychiatry Res. Aug 30; 193(2):85-92.

Bruins, J., Hijman, R., Van Ree, J.M. (1992) Effect of a single dose of des-glycinamide-[Arg8]vasopressin or oxytocin on cognitive processes in young healthy subjects. Peptides. May-Jun;13(3):461-8.

Bufkin, J.L. & Luttrell, V.R. (2005): Neuroimaging studies of aggressive and violent behavior: Current findings and implications for criminology and criminal justice. Trauma Violence Abuse 6:176 –191.

Bushman, B.J. & Anderson, C.A. (2001) Is it time to pull the plug on the hostile versus instrumental aggression dichotomy? Psychol Rev. Jan; 108 (1) 273-279.

Buss, A.H. & Perry, M. (1992): The aggression questionnaire. J Personality Soc Psychol; 63: 452–459.

Cadoret, R.J., O'Gorman, T.W., Troughton, E.,& Heywood, E. (1985). Alcoholism and antisocial personality. Interrelationships, genetic and environmental factors. Ach Gen Psychiatry 42: 161-167.

Camerer, C.F. (2003) Behavioural studies of strategic thinking in games. Trends Cogn Sci. May;7(5):225-231.

Carre´, J.M. & McCormick, C.M. (2008) Aggressive behavior and change in salivary testosterone concentrations predict willingness to engage in a competitive task. Horm Behav. Aug;54(3):403-9.

Carre´, J.M., Putnam, S.K. 7 McCormick, C.M. (2009) Testosterone responses to competition predict future aggressive behaviour at a cost to reward in men. Psychoneuroendocrinology. May;34(4):561-70.

Carre´, J.M., Gilchrist, J.D., Morrissey, M.D. & McCormick, C.M. (2010) Motivational and situational factors and the relationship between testosterone dynamics and human aggression during competition. Biol Psychol. May;84(2):346-53.

Carré, J.M., McCormick, C.M., & Hariri, A.R. (2011) The social neuroendocrinology of human aggression. Psychoneuroendocrinology. Aug;36(7):935-44.

Carter, C.S. (1992). Oxytocin and sexual behavior. Neurosci. Biobehav. Rev. 16:131–44

Carter, C.S., De Vries, A.C. & Getz, L.L. (1995) Physiological substrates of mammalian monogamy: the prairie vole model. Neurosci Biobehav Rev. Summer;19(2):303-14.

Carte, C.S. (2003) Developmental consequences of oxytocin. Physiol Behav . Aug;79(3):383-97.

Carter, C.S., Grippo, A.J., Pournajafi-Nazarloo, H., Ruscio, M.G. & Porges, S.W. (2008) Oxytocin, vasopressin and sociality. Prog Brain Res. 170:331-6.

Carter, C.S. (2014) Oxytocin pathways and the evolution of human behavior. Annu Rev Psychol. 65:17-39

Campbell, A. & Hausmann, M. (2013) Effects of oxytocin on women's aggression depend on state anxiety. Aggress Behav. Jul-Aug; 39(4): 316-322.

Chang, S., Barter, J., Ebitz, R., Watson, K., & Platt, M. (2012). Inhaled oxytocin amplifies both vicarious reinforcement and self-reinforcement in rhesus macaques (Macaca mulatta). Proc. Natl. Acad. Sci. U S A 109, 959–964

Cherek, D.R., Spiga, R., Steinberg, J.L., & Kelly, T.H. (1990) Human aggressive responses maintained by avoidance and escape from point loss. J Exp Anal of Behav. Mar; 53 (2): 293-303.

Cherek D.R. (1992) Point-subtraction aggression paradigm. University of Texas, Houston

Cherek, D.R., Moeller, F.G., Schnapp, W., & Dougherty, D.M. (1997) Studies of violent and non-violent male parolees I. Laboratory and psychometric measurements of aggression. Biol Psychiatry. 41, 514-522.

Cherek, D.R. & Lane, S.D. (1999) Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. Psychopharmacology. Oct; 146(4):473-481.

Cherek, D.R. & Lane, S.D. (2001) Acute effects of D-fenfluramine on simultaneous measures of aggressive escape and impulsive responses of adult males with and without a history of conduct disorder. Psychopharmacology (Berl). Sep;157(3):221-7.

Cherek, D.R., Lane, S.D., Pietras, C.J., & Steinberg, J.L. (2002a) Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. Psychopharmacology (Berl). Jan;159(3):266-74. Epub 2001 Oct 12.

Cherek, D.R., Lane, S.D., Pietras, C.J., Sharon, J., & Steinberg, J.L. (2002b) Acute effects of baclofen, a gamma-aminobutyric acid-B agonist, on laboratory measures of aggressive and escape responses of adult male

parolees with and without a history of conduct disorder. Psychopharmacology(Berl). Nov;164(2):160-7.

Cherek, D.R., Pietras, C.J., & Lane, S.D. (2003): Laboratory Measures: Point Subtraction Aggression Paradigm (PSAP). In E. Coccaro (Ed.), Aggression: Assessment and Treatment. (pp 215-228). New York: Marcel Dekker.

Cherek, D.R., Tcheremissine, O.V., & Lane, S.D. (2006). Psychopharmacology of aggression. In R.J. Nelson (Ed.). Biology of Aggression (pp 424-446). Oxford University Press, Oxford, UK.

Corder, G.W. & Foreman, D.I. (2009). Nonparametric Statistics for Non-Statisticians: A Step-by-Step Approach. Somerset, NJ: Wiley.

Dabbs, J.M., Carr, T.S., Frady, R.L., & Raid, K.J (1995) Testosterone, crime, and misbehavior among 692 male prison inmates Personal Individ Diff Vol 18, Issus 5, May, Pages 627–633.

Dahlberg, L.L. (2007) Public health and violence: Moving forward in a global context. In D.J. Flannery, A.T. Vazsoonyi & I.D. Waldman (Eds.), The Cambridge Handbook of Violent and Aggression. New York, Cambridge University Press.

Davidson, R.J., Putnam, K.M., & Larson, C.L. (2000): Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence. Science. 289:591–594.

Dawes, M.A., Tarter, R.E. & Kirisci, L. (1997) Behavioral self-regulation: correlates and 2 year follow-ups for boys at risk for substance abuse. Drug Alcohol Depend. May 2;45(3):165-76.

de Almeida, R.M., Ferrari, P.F., Parmigiani, S., Miczek, K.A. (2005) Escalated aggressive behavior: dopamine, serotonin and GABA. Eur J Pharmacol. Dec 5;526(1-3):51-64.

De Dreu, C.K., Greer, L.L., Handgraaf, M.J., Shalvi, S., Van Kleef, G.A., Baas, M., Ten Velden, F.S., Van Dijk, E., & Feith, S.W. (2010) The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans Science. Jun 11;328(5984):1408-11.

De Dreu, C.K., Shalvi, S., Greer, L.L., Van Kleef, G.A., & Handgraaf, M.J. (2012) Oxytocin motivates non-cooperation in intergroup conflict to protect vulnerable in-group members. PLoS One, 7(11):e46751.

Dickey, B., Normand, S.L., Weiss, R.D., Drake, R.E., & Azeni, H. (2002) Medical morbidity, mental illness, and substance use disorders. Psychiatr Serv. Jul;53(7):861-7.

DiMascio, A. (1973) The effects of benzodiazepines on aggression: reduced or increased? Psychopharmacologia 30:95–102 6.

Dinwiddie, S.H. (1992). Psychiatric disorders among wife batterers. Compr Psychiatry 33: 411-41

Dinwiddie, S.H. & Bucholz, K.K.(1993). Psychiatric diagnoses of self-reported child abusers. Child Abuse.

Dölen, G., Darvishzadeh, A., Huang, K.W., & Malenka, R.C. (2013) Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature. Sep 12; 501 (7466):179-84.

Domes, G, Heinrichs, M,, Michel, A,, Berger, C, & Herpertz, S.C.(2007a) Oxytocin improves "mind-reading" in humans. Biol Psychiatry. Mar 15;61(6):731-3. Epub 2006 Nov 29.

Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D.F. & , Herpertz, S.C. (2007b) Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol Psychiatry. Nov 15;62(10):1187-90.

Donaldson, Z.R. & Young, L.J. (2008) Oxytocin, vasopressin, and the neurogenetics of sociality. Science. Nov 7;322(5903):900-4.

Donegan, N.H., Sanislow, C.A., Blumberg, H.P., Fulbright, R.K., Lacadie, C., Skudlarski, P., Gore, J.C., Olson, I.R., McGlashan, T.H., & Wexler, B.E. (2003) Amygdala hyper-reactivity in borderline personality disorder implications for emotional dysregulation. Biol Psychiatry; 54:1284–1293.

Ebstein, R.P., Knafo, A., Mankuta, D., Chew, S.H., & Lai, P.S. (2012) The contributions of oxytocin and vasopressin pathway genes to human behavior. Horm Behav. Mar;61(3):359-79.

Ebitz, R.B. & Platt, M.L. (2014) An evolutionary perspective on the behavioral consequences of exogenous oxytocin application. Front Behav Neurosci. Jan 17;7:225.

Evans, J.J., Reid, R.A., Wakeman, S.A., Croft, L.B., & Benny, P.S. (2003) Evidence that oxytocin is a physiological component of LH regulation in non-pregnant women. Hum Reprod. Jul, 18 (7): 1428-31.

Evans, S., Shergill, S.S., & Averbeck, B.B. (2010) Oxytocin decreases aversion to angry faces in an associative learning task. Neuropsychopharmacology. Dec;35(13):2502-9.

Eronen, M., Hakola, P., & Tiihonen, J. (1996). Mental disorders and homicidal behavior in Finland. Arch Gen Psychiatry53: 497-501.

Febo, M., Numan, M., & Ferris, C.F. (2005) Functional magnetic resonance imaging shows oxytocin activates brain region associated with mother-pup bonding during suckling. J Neurosci. Dec, 14, 35(50) 11637-11644.

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B. (1996) Structured clinical interview for DSM-IV axis I disorders-patient edition, Biometrics Research Department, New York State Psychiatric Institute, New York.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B, & Benjamin, L. (1997) Structured clinical interview for DSM-IV axis II personality disorders (SCID-II), Biometrics Research Institute, New York State Psychiatric Institute, New York.

Fehr, E. & Fischbacher, U. (2003) The nature of human altruism. Nature. Oct 23;425(6960):785-91.

Gamer, M., Zurowski, B., & Büchel, C. (2010) Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. Proc Natl Acad Sci U.S.A. May 18; 107 (20): 9400-9405.

Gibbons, J.L., Barr, G.A., Bridger, W.H., & Leibowitz, S.F. (1979) Manipulations of dietary tryptophan: effects on mouse killing and brain serotonin in the rat. Brain Res. Jun 15;169(1):139-53.

Gimpl, G. & Fahrenholz, F. (2001) The oxytocin receptor System: structure, function, and regulation. Physiol Rev. 81, 2, 629-683.

Goyer, P.F., Andreason, P.J., Semple, W.E., Clayton, A.H., King, A.C., Compton-Toth, B.A., Schulz, S.C. & Cohen, R.M. (1994) Positron-emission tomography and personality disorders. Neuropsychopharmacology, 10:21-28.

Gowin, J.L., Swann, A.C., Moeller, F.G., & Lane, S.D. (2010) Zolmitriptan and human aggression: interaction with alcohol. Psychopharmacology (Berl). Jul;210(4):521-31

Gowin, J.L., Green, C.E., Alcorn, J.L., Swann, A.C., Moeller, F.G., & Lane, S.D. (2012) Chronic tiagabine administration and aggressive responding in individuals with a history of substance abuse and antisocial behavior. J Psychopharmacol. Jul;26(7):982-93.

Gowin, J.L., Green, C.E., Alcorn III, J.L., Swann, A.C., Moeller, F.G., & Lane, S.D. (2013) The role of cortisol and psychopathy in the cycle of violence. Psychopharmacology (Berl). Jun;227(4):661-72.

Green, M.J & Phillips, M.L. (2004): Social threat perception and the evolution of paranoia. Neurosci Biobehav Rev 28:333–342.

Grubbs F. (1969) Procedures for Detecting Outlying Observations in Samples, Technometrics, 11(1), 1-21.

Guastella, A.J., Mitchell, P.B., & Dadds, M.R. (2008) Oxytocin increases gaze to the eye region of human faces. Biol Psychiatry. 63: 3-5.

Guastella, A.J., Einfeld, S.L., Gray, K.M., Rinehart, N.J., Tonge, B.J., Lambert, T.J., & Hickie, I.B. (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry. Apr 1;67(7):692-4.

Hare, R.D. (1996). Psychopathy — a clinical construct whose time has come. Criminal Justice and Behavior 231, 25–54.

Hare, R.D., & Neumann, C.S. (2008): Psychopathy as a clinical and empirical construct. Annu Rev Clin Psychol; 4: 217-246.

Hempill, J.F., Hare, R.D. & Wong, S. (2011) Pscyhopathy and recidivism: A Review. Legal and Criminological Pscyhology. Feb: 3 (1): 139-170.

Heinz, A.J., Beck, A., Meyer-Lindenberg, A., Sterzer, P., & Heinz, A. (2011) Cognitive and neurobiological mechanisms of alcohol-related aggression. Nat Rev Neurosci. Jun 2;12(7):400-13.

Herpetz, S.C., Dietrich, T.M., Wenning, B., Krings, T., Eberich, S.G., Willmes. K., Thorn, A., & Sass, H (2001) Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biol Psychiatry; 50:292–298

Hicks, C., Ramos, L., Reekie, T., Misagh, G.H., Narlawar, R., Kassiou, M., & McGregor, I.S. (2014) Body temperature and cardiac changes induced by peripherally administred oxytocin, vasopressin and non-peptide

oxytocin receptor agonist WAY 267, 464: biotelemetry study in rats. Brit J Pharmacol.

Higley, J.D., Mehlman, P.T., Taub, D.M., Higley, S.B., Suomi, S.J., Vickers, J.H., & Linnoila, M. (1992) Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. Arch Gen Psychiatry. Jun;49(6):436-41.

Higley, J.D., Mehlman, P.T. , & Higley, S.B., Fernald, B., Vickers, J., Lindell, S.G., Taub, D.M., Suomi, S.J., & Linnoila, M. (1996a). Excessive mortality in young free-ranging male nonhuman primates with low cerebrospinal fluid 5 hydroxyindoleacetic acid concentrations. Arch. Gen. Psychiatry 53: 537–543.

Higley, J.D., King, S.T. Jr, Hasert, M.F., Champoux, M., Suomi, S.J., & Linnoila, M. (1996b) Stability of interindividual differences in serotonin function and its relationship to severe aggression and competent social behavior in rhesus macaque females. Neuropsychopharmacology. Jan;14(1):67-76.

Hirschenhauser, K., Taborsky, M., Oliveira, T., Canàrio, A.V.M., & Oliveira, R.F. (2004) A test of the ‘challenge hypothesis’ in cichlid fish: simulated partner and territory intruder experiments. Anim Behav. Vol. 68, Iss.4, October, Pages 741–750

Insel, T.R. & Shapiro, L.E. (1992) Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc Natl Acad Sci U S A. Jul 1;89(13):5981-5.

Iversen, I.H. (1991). Methods of analyzing behavior patterns. In I.J Iversen & K.A. Lattal (Ed.), Techniques in the Behavioral and Neural Sciences: Experimental Analysis of Behavior Part 2 (pp. 193- .242). New York, NY: Elsevier Science Publishing Co., Inc.

Jesso, S., Morlog, D., Ross, S., Pell, M.D., Pasternak, S.H., Mitchell, D.G., Kertesz, A., Finger, E.C. (2011) The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. Brain. Sep;134(Pt 9):2493-501.

Kalmoe, N.P. (2014) Trait aggression in two representative U.S. surveys: Testing the generalizability of college samples. Aggress Behav. Jul 2.

Kemp, A.H., Quintana, D.S., Kuhnert, R.L., Griffiths, K., Hickie, I.B., & Guastella, A.J. (2012) Oxytocin increases heart rate variability in humans at rest: implications for social approach-related motivation and capacity for social engagement. PLoS One. 7 (8):e44014.

Kessler, R.C., Coccaro, E.F., Fava, M., Jaeger, S., Jin, R., & Walters, E. (2006). The prevalence and correlates of DSM-IV intermittent explosive disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 63: 669-678.

Kiehl, K.A. (2006) A cognitive neuroscience perspective on psychopathy: evidence for paralimbic system dysfunction. Psychiatry Res. Jun 15;142(2-3):107-28.

Kirkpatrick, M.G., Lee, R., Wardle, M.C., Jacob, S., & de Wit, H. (2014) Effects of MDMA and Intranasal oxytocin on social and emotional processing. Neuropsychopharmacology. Jun;39(7):1654-63.

Kiss, A. & Mikkelsen, J.D. (2005) Oxytocin--anatomy and functional assignments: a minireview. Endocr Regul. Sep; 39 (3):97-105.

Koehbach, J., Stockner, T., Bergmayr, C., Muttenthaler, M., & Gruber, C.W. (2013) Insights into the molecular evolution of oxytocin receptor ligand binding. Biochem Soc Trans. Feb 1;41(1):197-204.

Koenigsberg, H.W., Prohovnik, I., Lee, H., Pizzarello, S., New, A.S., & Siever, L.J (2007) Neural correlates of the processing of negative and positive social scenes in borderline personality disorder (abstract). Biol Psychiatry 2007; 61:104s

Kosfeld, M., Neinrichs, M., Zak, P.J., Fischbacher, U., & Fehr, E. (2005) Oxytocin increases trust in humans. Nature. June 2; 435 (7042): 673-676.

Kouri, E.M., Lukas, S.E., Pope, H.G. Jr, & Oliva, P.S. (1995) Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. Drug Alcohol Depend. Nov;40(1):73-9.

Krakowski, M. (2003) Violence and serotonin: influence of impulse control, affect regulation, and social functioning. J Neuropsychiatry Clin Neurosci. Summer;15(3):294-305.

Lane, S.D. & Cherek, D.R. (2000). Biological and behavioral investigation of aggression and impulsivity. In D.H. Fishbein (Ed.), The science, treatment and prevention of antisocial behavior: applications to the criminal justice system. (pp. 5.1-5.21). Kingston, NJ: Civic Research Institute.

Lane, S.D. , Cherek, D.R., & Nouvion, S.O. (2008). Modulation of human risky decision making by flunitrazepam. Psychopharmacology (Berl) Feb;196(2):177-88. Epub 2007 Oct 5.

Lane, S.D. & Gowin, J.L. (2009) GABAergic modulation of human social interaction in a prisoner's dilemma model by acute administration of alprazolam. Behav Pharmacol. Oct;20(7):657-61.

Lee, H.J., Macbeth, A.H., Pagani, J.H., & Young III, W.S.. (2009a) Oxytocin: the great facilitator of life. Prog in Neurobiol, Jun, 88 (2): 127-151.

Lee, R., Ferris, C. , Van de Kar, L.D., & Coccaro, E.F. (2009b) Cerebrospinal fluid oxytocin, life history of aggression, and personality disorder. Psychoneuroendocrinology. 34, 1567-1573.

Lee, A.G., Cool, D.R., Grunwald ,W.C. Jr, Neal, D.E., Buckmaster, C.L., Cheng, M.Y., Hyde, S.A., Lyons, D.M. & Parker, K.J. (2011) A novel form of oxytocin in New World monkeys. Biol Lett. Aug 23;7(4):584-7.

Leistico, A.M., Salekin, R.T., DeCoster, J., & Rogers, R. (2008) A large-scale meta-analysis relating the hare measures of psychopathy to antisocial conduct. Law Hum Behav, Feb, Vol 32(1), 28-45.

Lieving, L.M., Cherek, D.R., Lane, S.D., Tcheremissine, O.V., & Nouvion, S.O. (2008) Effects of acute tiagabine administration on aggressive responses of adult male parolees. J Psychopharmacol. 2008 Mar;22(2):144-52.

Linnoila, M., Virkkunen, M., Scheinin, M., Nuutila, A., Rimon, R., & Goodwin, F.K. (1983). Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. Life Sci 33:2609–2614.

Lorber, M.F. (2004) Psychophysiology of aggression, psychopathy, and conduct problems: a meta-analysis. Psychological Bulletin. Jul; 130 (4): 531-552.

Ludwig, M. & Leng, G. (2006) Dendritic peptide release and peptide-dependent behaviours. Nat Rev Neurosci. Feb; 7 (2): 126-36.

MacDonald, E., Dadds, M.R., Brennan, J.L., Williams, K., Levy, F., & Cauchi, A.J. (2011) A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. Psychoneuroendocrinology. Sep;36(8):1114-26.

Mahmut, M.K., Menictas, C., Stevenson, R.J., & Homewood, J. (2011) Validating the factor structure of the Self-Report Psychopathy scale in a community sample. Psychological Assessment; 23: 670 -768

Malik, A.I, Zai, C.C., Abu, Z., Nowrouzi, B., & Beitchman, J.H. (2012) The role of oxytocin receptor gene variants in childhood-onset aggression. Genes Brain Behav. Jul; 11 (5): 545-551.

Mazur, A., 1985. A biosocial model of status in face-to-face primate groups. Soc. Forces 64, 377—402.

Mehlman, P.T., Higley, J.D., Faucher, I., Lilly, A.A., Taub, D.M., Vickers, J., Suomi, S.J., & Linnoila, M. (1994) Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. Am J Psychiatry. Oct;151(10):1485-91.

Meyer-Lindenberg, A., Domes, G., Kirsch, P., & Heinrichs, M. (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat Rev Neurosci. Aug 19; 12 (9): 524-538.

Meyer-Lindenberg, A. & Tost, H. (2012) Neural mechanisms of social risk for psychiatric disorders. Nat Neurosci. 2012 Apr 15;15(5):663-8.

Miczek, K,A., Fish, E.W., De Bold, J.F., & de Almeida, R.M. (2002) Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and gamma-aminobutyric acid systems. Psychopharmacology (Berl). Oct; 163(3-4):434-58.

Miczek, K.A., Fish, E.W., De Almeida, R.M., Faccidomo, S., & Debold ,J.F. (2004a) Role of alcohol consumption in escalation to violence. Ann N Y Acad Sci. Dec;1036:278-89.

Miczek, K.A., Faccidomo, S., de Almeida, R.M., Bannai, M., Fish, E.W., & Debold, J.F. (2004b) Escalated aggressive behavior: new pharmacotherapeutic approaches and opportunities. Ann N Y Acad Sci. Dec;1036:336-55.

Minzenberg, M.J., Fan, J., New, A.S., Tang, C.Y., & Siever. L.J. (2007) Front-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res; 155:231–243.

Moeller, F.G., Dougherty, D.M., Swann, A.C., Collins, D., Davis ,C.M., & Cherek, D.R. (1996) Tryptophan depletion and aggressive responding in healthy males. Psychopharmacology (Berl). Jul;126(2):97-103.

Moeller, F.G., Dougherty, D.M., Rustin, T., Swann, A.C., Allen, T.J., Shah, N., & Cherek, D.R. (1997) Antisocial personality disorder and aggression in recently abstinent cocaine dependent subjects. Drug Alcohol Depend. Mar 14;44(2-3):175-82.

Moeller, F.G., Dougherty, D.M., Lane, S.D., Steinberg, J.L., & Cherek, D.R. (1998) Antisocial personality disorder and alcohol-induced aggression. Alcoholism: Clinical and Experimental Research. Dec;22(9):1898-902.

Mokros, A., Menner, B., Eisenbarth, H., Alpers, G.W., Lange, K.W., & Osterheider, M. (2008) Diminished cooperativeness of psychopaths in a prisoner's dilemma game yields higher rewards.J Abnorm Psychol. May;117(2):406-13.

Molina, V., Ciesielski, L., Gobaille, S., Isel, F., & Mandel, P. (1987) Inhibition of mouse killing behavior by serotonin-mimetic drugs: effects of partial alterations of serotonin neurotransmission. Pharmacol Biochem Behav. May;27(1):123-31.

Moore, T.M., Scarpa, A., & Raine, A. (2002) A Meta-Analysis of Serotonin Metabolite 5-HIAA and Antisocial Behavior. Aggress Behav. Volume 28, Issue 4, pages

Muller. M.N. & Richard, W.W. (2004) Dominance, aggression and testosterone in wild chimpanzees: a test of the 'challenge hypothesis'. Anim Behav. Vol 67, Jan (1):113–123299–316.

Neumann, C.S., Schmitt, D.S., Carter, R., Embley, I., & Hare, R.D. (2012) Psychopathic traits in females and males across the globe. Behav Sci Law. Sep-Oct;30(5):557-74.

Neumann, I.D. & Landgraf, R. (2012) Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci. Nov;35(11):649-59.

Newman, W.J. (2012) Psychopharmacologic management of aggression. Psychiatr Clin North Am. Dec;35(4):957-72.

Norman, G.J., Cacioppo, J.T., Morris, J.S., Malarkey, W.B., Berntson, G.G., & Devries, A.C. (2011) Oxytocin increases autonomic cardiac control: moderation by loneliness. Biol Psychol. Mar; 86 (3): 174-180.

Nouvion, S.O., Cherek, D.R., Lane, S.D., Tcheremissine, O.V. & Lieving, L.M. (2007) Human proactive aggression: Association with personality disorders and psychopathy. Aggress Behav.Vol. 33, 552-562.

Pajer, K.A. (1998). What happens to "bad" girls? A review of the adult outcomes of antisocial adolescent girls. Am J Psychiatry 155:862-870.

Passamonti, L., Crockett, M.J., Apergis-Schoute, A.M., Clark, L., Rowe, J.B., Calder, A.J., & Robbins, T.W. (2012) Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. Biol Psychiatry. Jan 1;71(1):36-43.

Patrick, C.J. (2008) Psychophysiological correlates of aggression and violence: an integrative review. Phil Trans Royal Soc B: Biol Sci. Aug 12; 363 (1503): 2543-2555.

Patrick, C.J. (2014) Physiological correlates of psychopathy, antisocial personality disorder, habitual aggression, and violence. Curr Top Behav Neurosci.;21:197-227.

Patterson, C. M., & Newman, J. P. (1993). Reflectivity and learning from aversive events: Toward a psychological mechanism for the syndromes of disinhibition. Psychol Rev, 100, 716–736

Patton, J.H., Stanford, M.S., & Barratt, E.S. (1995): Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol; 51: 768–774.

Paulhus, D.L., Neuman, C.F., & Hare, R.D. (2010): Manual for the Self-Report Psychopathy Scale. Toronto: Multi-Health Systems.

Payla, W.L. (1992) Dynamics in the fine structure of schedule-controlled behavior. J Exp Anal Behav. May;57(3):267-87.

Pedersen, C.A., Smedley, K.L., Leserman, J., Jarskog, L.F., Rau, S.W., Kampov-Polevoi, A., Casey, R.L., Fender, T., Garbutt, J.C. (2013) Intranasal oxytocin blocks alcohol withdrawal in human subjects. Alcohol Clin Exp Res. Mar;37(3):484-9.

Petersson, M., Alster, P., Lundeberg, T., & Uvnäs-Moberg, K. (1996). Oxytocin causes a long-term decrease of blood pressure in female and male rats. Physiol. Behav. 60, 1311–1315.

Placidi, G.P., Oquendo, M.A., Malone, K.M., Huang, Y.Y., Ellis, S.P., & Mann, J.J. (2001) Aggressivity, suicide attempts, and depression: relationship to cerebrospinal fluid monoamine metabolite levels. Biol Psychiatry. 2001 Nov 15;50(10):783-91.

Potegal, M., Hebert, M., DeCoster, M., & Meyerhoff, J.L. (1996) Brief, high frequency stimulation of the corticomedial amygdala induces a delayed and prolonged increase of aggressiveness in male Syrian golden hamsters. Behav Neurosci. Apr;110(2):401-12.

Rachlin, H. & Locey, M. (2011) A behavioral analysis of altruism. Behav Processes. May;87(1):25-33.

Raine A, Buchsbaum M, & LaCasse L (1997). Brain abnormalities in murderers indicated by positron emission tomography. Biol Psychiatry 42: 495-508.

Raine, A., Meloy, J.R., Bihrle, S., Stoddard, J., LaCasse, L., & Buchsbaum, M.S. (1998a). Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav Sci Law, 16: 319-332.

Raine, A., Stoddard, J., Bihrle, S., & Buchsbaum, M. (1998b). Prefrontal glucose deficits in murderers lacking psychosocial deprivation. Neuropsychiatry, Neuropsychol, Behav Neurol, 11: 1-7.

Rasmussen, K. & Levander, S. (1996) Symptoms and personality characteristics of patients in a maximum security psychiatric unit. International J Law Psychiatry. 19: 27-37.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., & Goodwin, F.K.(1990). Comorbidity of Mental- Disorders with Alcohol and Other Drug-Abuse - Results from the Epidemiologic Catchment-Area (EGA) Study. JAMA 264: 2511-2518.

Rilling, J.K., Glenn, A.L., Jairam, M.R., Pagnoni, G., Goldsmith, D.R., Elfenbein, H.A., & Lilienfeld, S.O. (2007) Neural correlates of social cooperation and non-cooperation as a function of psychopathy. Biol Psychiatry. Jun 1;61(11):1260-71.

Rilling, J.K & Sanfet, A.G. (2011) The neuroscience of social decision-making. Annu Rev Psychol.62:23-48.

Rilling, J.K., DeMarco, A.C., Hackett, P.D., Thompson, R, Ditzen, B., Patel, R., & Pagnoni, G. (2012) Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. Psychoneuroendocrinology. 37 (4): 447-461.

Ross, H.E., Cole, C.D., Smith, Y., Neumann, I.D., Landgraf, R., Murphy, A.Z., & Young, L.J. (2009) Characterization of the oxytocin system regulating affiliative behavior in female prairie voles. Neuroscience. 2009 Sep 15;162(4):892-903.

Rush, C.R., Stoops, W.W., Lile, J.A., Glaser, P.E., & Hays, L.R. (2011) Subjective and physiological effects of acute intranasal methamphetamine during d-amphetamine maintenance. Psychopharmacology (Berl). Apr;214(3):665-74.

Saltzman, W. & Maestripieri, D. (2011) The neuroendocrinology of primate maternal behavior. Progress in Neuro-psychopharmacology and Biological Psychiatry. Jul 1; 35 (5): 1192-1204.

Schmahl, C.G., Vermetten, E., Elzinga, B.M., & Bremner, J.D. (2003) Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. Psychiatric Res; 122:193–198

Sevak, R.J., Stoops, W.W., Hays, L.R. & Rush, C.R. (2009) Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate, and triazolam in methamphetamine-trained humans. J Pharmacol Exper Therap. Mar; 328 (3): 1007-1018.

Shacham, S. (1983). A shortened version of the Profile of Mood States. Journal of Personality Assessment, 47, 305-306.

Shahrestani, S., Kemp, A.H., & Guastella, A.J. (2013) The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis.Neuropsychopharmacology. Sep;38(10):1929-36.

Shamay-Tsoory, S.G., Fischer, M., Dvash, J., Harai, H., Perach-Bloom, N., & Levkovitz, Y. (2009) Intranasal administration of oxytocin increases envy and schadenfreude (gloating). Biol Psychiatry, Nov 1; 66(9): 864-870.

Shipley, W. C., Gruber, C.P., Martin, T.A., & Klein, A.M. (2009) Shipley-2: Manual. Western Psychological Services. Los Angeles.

Siever, L.J. (2008) Neurobiology of violence. Am J Psychiatry. Apr; 165(4):429-442.

Simeon, D., Bartz, J., Hamilton, H., Crystal, S., Braun, A., Ketay, S., & Hollander, E. (2011) Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. Psychoneuroendocrinology. Oct; 36(9): 1418-1421.

Soma, K.K. (2006) Testosterone and Aggression: Berthold, Birds and Beyond. J Neuroendocrinol. July ; 18(7): 543–551.

Stanford, M.S., Houston, R.J., Mathias, C.W., Villemarette-Pittman, N.R., Helfritz, L.E., & Conklin, S.M. (2003) Characterizing aggressive behavior. Assessment. 10: 183–190.

Stoops, W.W., Blackburn, J.W., Hudson, .D.A., Hays, L.R., & Rush, C.R (2008) Safety, tolerability and subject-rated effects of acute intranasal cocaine administration during atomoxetine maintenance. Drug Alcohol Depend. Jan 1;92(1-3):282-5.

Stoops, W.W., Lile, J.A., Glaser, P.E., Hays, L.R., & Rush, C.R. (2012) Alternative reinforcer response cost impacts cocaine choice in humans. Prog Neuro-Psychopharmacol Biol Psychiatry. Jan 10;36(1):189-93.

Striepens, N., Scheele, D., Kendrick, K.M., Becker, B., Schäfer, L., Schwalba, K., Reul, J., Maier, W., & Hurlemann, R. (2012) Oxytocin facilitates protective responses to aversive social stimuli in males. Proc Natl Acad Sci. Oct 30; 109 (44): 18144-18149.

Swann, A.C., Lijffijt, M., Lane, S.D., Steinberg, J.L., & Moeller, F.G. (2010) Interactions between bipolar disorder and antisocial personality disorder in trait impulsivity and severity of illness. Acta Psychiat Scand121: 453-461.

Takahashi, A., Quadros, I.M. de Almeida, R.M., & Miczek, K.A. (2012) Behavioral and pharmacogenetics of aggressive behavior. Curr Top Behav Neurosci. Feb 2.

Tukey, J. (1949) Comparing Individual Means in the Analysis of Variance. Biometrics, Vol. 5, No. 2Jun., pp. 99-114

Tukey, J.W. (1980). We need both exploratory and confirmatory. Am Stat 34 (1): 23–25.

Yildirim, B.O. & Derksen, J.J. (2012a) A review on the relationship between testosterone and the interpersonal/affective facet of psychopathy. Psychiatry Res. May 30;197(3):181-98.

Yildirim, B.O. & Derksen, J.J. (2012b) A review on the relationship between testosterone and life-course persistent antisocial behavior. Psychiatry Res. Dec 30;200(2-3):984-1010.

Young, L.J., Murphy Young, A. Z., & Hammock, R.A. (2005) Anatomy and neurochemistry of the pair bond. J Comp Neurol. Dec 5;493(1):51-7.

Virkkunen, M. (1979). Alcoholism and antisocial personality. Acta Psychiat. Scand., 59: 493-501.

Volkow, N.D., Tancredi, L.R., Grant, C., Gillespie, H., Valentine, A., Mullani, N., Wang, G., & Hollister, L (1995).Brain glucose metabolism in violent psychiatric patients: a preliminary study. Psychiatry Res, 61: 243-253.

Wingfield, J., Hegner, R., Dufty, A., Ball, G., 1990. The 'challenge hypothesis': Theoretical implications for patterns of testosterone secretion, mating systems, and breeding strategies. Am. Nat. 136, 829—846

Winslow, J.T. & Insel, T.R. (1991) Social status in pairs of male squirrel monkeys determines the behavioral response to central oxytocin administration. J Neurosci. Jul;11(7):2032-8.

Williams, J.R., Catania, K. &Carter, C.S. (1992). Development of partner preferences in female prairie voles (Microtus ochrogaster): the role of social and sexual experience. Horm. Behav. 26:339–493-69.

Williams, J.R., Insel, T.R., Harbaugh, C.R. & Carter, C.S. (1994). Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles. J. Neuroendocrinol. 6:247–50.

Widom, C.S. (1989) The cycle of violence Science. Apr 14;244(4901):160-6.

Winslow, J.T., Noble, P.L., Lyons, C.K., Sterk, S.M., & Insel, T,R. (2003) Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. Neuropsychopharmacology, 28, 910–918, advance online publication, 26 March 2003.

Young, L.J. (2009) Being human: love: neuroscience reveals all. Nature. Jan 8;457(7226):148.

Young, K.A., Gobrogge, K.L., Liu, Y., & Wang, Z. (2011) The neurobiology of pair bonding: Insights from a socially monogamous rodent. Front Neuroendocrinol. 32, 53-69.

Zak, P.J., Stanton, A.A., & Ahmadi, S. (2007) Oxytocin increases generosity in humans. PLoS One, Nov 7; 2 (11): e1128.

VITA

Joseph Louis Alcorn III was born on February 12th, 1987, the son of Maria Dolores Hernandez and Joseph Louis Alcorn Jr. After graduating from Kempner High School, in Sugar Land, Texas in 2005, he entered The University of North Texas (UNT). He graduated cum laude with the degree of Bachelor of Science with a major in Psychology from UNT in May of 2009. In August of 2009, he enrolled in the Graduate School of Biomedical Sciences at The University of Texas Health Science Center at Houston (UTHSC) to begin work on his doctorate in Neuroscience under the advisement of Scott D. Lane, Ph.D. Upon completion of his Ph.D., he plans continue conducting research in the fields of behavioral pharmacology in a post-doctoral research fellowship at the University of Kentucky under the mentorship of Craig R. Rush, Ph.D. and William Stoops, Ph.D.

Permanent address:

14231 Silver Glade Ln

Sugar Land, TX 77498